

ANNALS OF INTERNAL MEDICINE

VOLUME 34

JUNE, 1951

NUMBER 6

THE INTEGRATIVE ACTION OF THE ENDOCRINE SYSTEM *

By J. H. MEANS, M.D., F.A.C.P.,† *Boston, Massachusetts*

FIRST, may I express my thanks for the honor you have done me in asking me to give your Harvard Lecture. For subject I have chosen certain aspects of the fundamental question, "What makes us tick?"

"What makes us tick as human beings" is perhaps relatively easy to answer. We might say the cerebral cortex or, if you prefer, the soul of man. The latter, however, gets us into theology, and I would prefer to stay out of that—at least at this time. "What makes us tick as animals" is a more complicated question. There is involved not only our cerebral cortex but our adrenal cortices as well, to say nothing of the rest, both of our nervous systems and of our endocrine systems.

The great dynamic integrative mechanisms of the animal body are the nervous and circulatory systems, and the endocrine system which employs the circulation as its conveyor. These systems, which are integrated with one another, together play an indispensable rôle in the integration of the higher animal in its entirety.

But, one may ask, "What of the amoeba?" This lowly being seemingly gets on well without either an endocrine or a nervous system, yet it behaves as a beautifully integrated organism, better perhaps in some respects than man. Who, for example, ever heard of a schizophrenic amoeba? Does the amoeba make substances bearing any resemblance to hormones, or does it get on quite well without them? I suspect that it gets on without them, and that integration in single celled existence is achieved through regulation of the rate of one enzyme system by the accumulated products of another enzyme system. We may call this enzymatic integration, or the primordial

* Received for publication January 5, 1951.

Third annual Harvard Lecture given at the University of Colorado Medical Center, December 8, 1950, under the auspices of the Rocky Mountain Harvard Medical Alumni Association.

† Jackson Professor of Clinical Medicine, Harvard University, and Chief of the Medical Services, Massachusetts General Hospital.

integration of the unicellular, and perhaps look upon it as the most primitive integrating mechanism of the multicellular. I will return to this interesting subject later.

When I was a medical student I read from cover to cover with rapt attention the work of Sherrington, then professor of physiology at Liverpool, entitled, "The Integrative Action of the Nervous System." It was his Silliman Lectures, delivered at Yale, and it represented the most authoritative work on the physiology of the nervous system of approximately half a century ago. Investigation since Sherrington's has added much to our understanding of the physiology of the nervous system, as, for example, the whole concept of the conditioned reflex of Pavlov, the chemical mediation of nerve impulse, localization of function in the brain, etc., but I believe there is little, if anything, in Sherrington's conceptual scheme that requires retraction.

This work, as I say, made a deep impression on me, and through the intervening years, as I have become increasingly interested in endocrinology, I have become more and more conscious of certain similarities between the functions of the nervous and endocrine systems.

In both systems stimuli are received; signals are sent to distant end-organs which, upon receipt thereof, perform in turn the functions they have been evolved to perform. "The unit mechanism in integration by the nervous system," Sherrington tells us, "is the reflex," and in the reflex there are involved "at least three separable structures": receptors, conductors and effectors. In the case of the nervous system, receptors are sense organs of one sort or another, conductors are neurones and synapses, and effectors are muscle, or gland cells. The same terminology can be applied to the endocrine system. Receptors are the cells of endocrine glands or similar tissues, conductors are hormones, and effectors are the end-organs or targets upon which hormones specifically act. The simplest nervous reflex arc involves at least two neurones, but more complicated reactions require many more. So also in the endocrine system we often find hook-ups in which two or more hormones are involved. An important property of the nervous system also is that action on effectors may in some cases be excitatory, in others, inhibitory. The same is true of the endocrine system. Hormone A, for example, provokes the delivery of hormone B, but hormone B suppresses that of hormone A.

I do not wish to belabor the nervous-endocrine analogy unduly—it has, of course, but a limited application—nor do I wish to consider integration by the endocrine system as a thing apart. However, if the limitations of the analogy are recognized (and I hope, if not already obvious, they will emerge as I proceed), it will prove helpful in the development of a concept of total integration of the person, which is what, after all, concerns the physician.

The whole process of living, in its material realm, consists in everlastingly adjusting to environment. Adjustment includes not merely the erection of defenses against hurtful influences of environment, but also the alteration

of environment by the organism to make it more suitable for the organism. Good adjustment is health; poor adjustment is illness. Successful adjustment is integration, unsuccessful is disintegration. When adjustment fails completely, life ceases or, if you prefer, death takes place. It is a case of "root hog, or die." Frustration I should classify as a form of disintegration.

"In the multicellular animal," Sherrington tells us, "especially for those higher reactions which constitute its behaviour as a social unit in the natural economy, it is nervous reaction which par excellence integrates it, welds it together from its components, and constitutes it, from a mere collection of organs, an animal individual."

Sherrington admits that the animal possesses other integrating agencies, for example, "the mechanical combination of the unit cells of the body into a single mass." Also, he speaks of integration resulting from chemical agencies, as, for example, that resulting from the circulation of the blood. But extra-nervous phenomena were not his concern, and he said nothing further about them.

At approximately the same time that I was reading Sherrington I also had the good fortune to have as teacher of physiology, Walter Bradford Cannon. At the time I was a medical student he was beginning his classic studies on the effect of the emotions on bodily processes, and the development of his concept of homeostasis. Unlike Sherrington, Cannon was concerned with both nervous and chemical, or endocrine, integrating mechanisms. He was less occupied with external behavior of the organism than with its methods of preserving the constancy of its internal environment, which Claude Bernard had recognized as the price of free and independent life. Therefore, he was more concerned with the vegetative, or autonomic, nervous system, which works inwardly on the viscera and governs internal environment, than with the central, which works outwardly; and of the two divisions of the autonomic nervous system he was more concerned with the sympathetic division, which discharges diffusely to the viscera, including blood vessels, than with the parasympathetic, which is focused more sharply on specific end-organs. In considering the integration of the nervous and the endocrine systems, one with the other, we shall have to take into account all divisions of the former, but in particular the sympathetic.

The endocrine system, like the nervous system, can be separated into certain divisions. On the one hand we have such organs as the adrenal medulla and the posterior pituitary (or neurohypophysis), which are clearly under direct neural control, and which even bear strong resemblances histologically to nervous tissue; while on the other we have the remaining, more obviously glandular, endocrine organs, which have not been proved to be under any direct neural control. I have been tempted to call the first category the para-endocrine system, to set it apart in our minds from all the rest of the endocrine system. The hormones of the para-endocrines—adrenaline and pituitrin—are quick acting and have widespread effects. They are secreted in response to stimuli reaching their parent cells directly

over autonomic nervous pathways. The hormones of the remaining endocrines are more sharply focused on their targets. They are secreted in response to humoral, not neural, stimulation.

In the organizational pattern of the endocrine system in its present state of evolution in vertebrates, we find what I have called the para-endocrine system, occupying an intermediary position between the nervous and the endocrine systems proper. All impulses—at least so it appears—that pass from the nervous system to the endocrine, and we know beyond all possible doubt that such passages occur, must pass by way of the para-endocrines, reaching the para-endocrine glands neurally; they continue humorally (or, if you prefer, hormonally), seemingly only via the anterior lobe of the pituitary. From the anterior pituitary the organizational pattern may be described, in part at least, as a congeries of two-way hormonal pathways (or axes) radiating from the anterior lobe to one of the peripheral endocrine organs. In each case the two-way pathway is traversed on the outward journey by a tropic hormone of the anterior-pituitary which stimulates the peripheral gland to make its hormone (or hormones), and on the return journey by the peripheral hormone, which in turn inhibits the pituitary with respect to that particular tropic function. This type of balanced reaction, which I shall call the axial principle, is semi-automatic, but not, as we shall see presently, completely independent unless it becomes so in disease. It may be looked upon as a functional unit of the endocrine system, analogous in some respects to the reflex arc of the nervous system. That the secretion by the pituitary of adenotropic hormones (that is, hormones whose targets are other endocrines) is controlled by the blood level of the hormones of the peripheral gland which is stimulated seems to be a fundamental law of the endocrine system. Knowledge of this law was first gained from the so-called castration phenomenon, that is to say, hypertrophy of the pituitary and increased secretion of the hormone tropic to the gonads which have been removed or destroyed. The phenomenon is well exemplified by the physiologic castration of the menopause, causing a great increase in secretion by the pituitary of gonadotropic hormone, which is responsible for the hot flashes characteristic of this endocrine event in the life of woman.

The axial principle is known to apply to the pituitary in its relation to the gonads, the thyroid and the adrenal cortices. So far as I have discovered, there is no convincing evidence that the pituitary exercises any tropic action over the parathyroids or pancreatic islands. It also should be noted that the anterior pituitary makes certain hormones which act directly on non-endocrine end-organs, as, for example, prolactin and the growth hormone.

The ascendancy which the anterior pituitary has gained over the endocrine system may be likened to that of the cerebral cortex over the nervous system. As the cerebral cortex signals various parts of the soma over pathways of varying numbers of neurones, so does the pituitary at times send a hormone to impinge directly on an effector target—a melanophore, for example, or a mammary gland—while at others, the ultimate somatic

target is reached via an intermediary endocrine, as pituitary to gonad to uterus, or pituitary to thyroid to muscle. In other words, the endocrines and their hormones may be coupled up as are neurones.

Whether there are important direct humoral balanced relationships between peripheral endocrines, one with another, not routed through or mediated by the anterior pituitary, I think is not known. Presumably there are what we may call non-specific effects, as when an increasing output of thyroid hormone directly causes an increased metabolic activity of the cells of other endocrines, along with all other cells of the body, for example, when the metabolism of the ovary is raised by thyroid together with that of the entire subject and, as a result, a sterile woman becomes fertile. But action of this sort would not be in the same category as the specific balanced relations between the anterior lobe and the peripheral glands. The latter may be likened to a nervous reaction originating in and requiring the presence of the higher nerve centers, the former to reflex nervous phenomena which remain intact in the spinal animal. One fact perhaps pertinent in this connection is that in the case of the thyroid at least, it can be shown that the gland's own hormone inhibits the gland directly. I have wondered if, phylogenetically speaking, this type of control of thyroid function might represent a more ancient one than that mediated through the pituitary.

For a complete understanding of the *modus operandi* of the endocrine system as it exists in man and his nearer relatives in the animal scale, I have long believed that more knowledge of the evolutionary process is needed. From what primitive form did it evolve? Early in the multicellular story, enzymatic or, as I called it earlier, primordial integration, may have sufficed, but only for very simple organisms living in very simple environments. As the struggle for survival has driven organisms into ever tougher environments, such superstructures as nervous and endocrine systems have of necessity been evolved in order to increase efficiency to the point where such environments can successfully be mastered.

In considering the nervous system, Sherrington discusses the nerve cell network of the jellyfish *Medusa*. Here is a nervous system which receives stimuli and promotes coördinated movement of the whole organism, yet is without polarity or centralization. There is neither head nor tail to such a system, yet it adequately brings about adjustment of this particular organism to its particular environment. As we ascend the animal scale, the nervous system develops a linear and segmental arrangement—a head end gains dominance, culminating in the brain of man. Similarly, may not the endocrine system have begun without the segregation of endocrine tissues into specific glands, and, when glands were first evolved, may they not have been in more or less equal partnership, one with the others, without any one member being dominant in the sense that the anterior pituitary is now dominant? As a matter of fact, when I was a medical student that is about the way the endocrine system was visualized. We spoke of the ductless glands, not of the endocrine system, and we visualized them as operating

pretty much as individuals. The present concept of what I have called the axial organization was quite unknown. The pituitary-thyroid axis, for example, did not enter our thinking on thyroid problems until after 1930, and then for some years we were rather inclined to conceive it as working pretty much as a self-regulating gadget, not much influenced from higher up.

Now, however, great interest is focused on the neuro-endocrine bridge, of which the anterior-pituitary seems to be the keystone—particularly, on the question as to what is the approach to this bridge from the nervous system side. As yet the evidence bearing on this question is, on the whole, rather scant. To be sure, as early as 1914 Cannon showed that stimulation of the splanchnic nerves of the sympathetic nervous system caused a discharge of adrenaline from the adrenal medulla; also it seems likely, though the evidence is less clear cut, that the neurohypophysis is stimulated to secretory activity by nervous impulses reaching it via the stalk from the hypothalamus; but when we search for evidence of a direct pathway, either neural or humoral, between the neurohypophysis and the adenohypophysis, we end up in confusion. It is true that various forms of psychic activity are followed by alteration in function of the peripheral endocrines, but by what route is far from clear. Indeed, one cannot be sure that the intimate proximity of the neurohypophysis to the adenohypophysis, or of the adrenal medulla to the adrenal cortex, has any functional significance at all. It is possible that these juxtapositions are purely adventitious. Since evidence of direct secretory innervation of endocrines, except adrenal medulla and neurohypophysis, is unconvincing, we may postulate that for stimulation of the other glands a neurohumoral pathway is requisite. In the case of one of them—the adrenal cortex—the pathway, thanks largely to the work of Long and his collaborators, has been elucidated. With evidence now available, this pathway may be traced as follows:

Afferent impulses from the outside world and the muscular system impinge, through sense organs, upon the thalamus. Thence they are relayed to the higher levels the brain, where they give rise to processes of cerebration, the emotional component of which activates the hypothalamus, which in turn excites the sympathetic nervous system, and with it, the adrenal medulla, with resulting discharge of adrenaline. Adrenaline, of course, has many and varied actions and a multiplicity of targets, among which, so Long's work suggests, is the adenohypophysis, which is stimulated to discharge adrenocorticotrophic hormone or, as it is now universally called, ACTH. Thus one might refer to adrenaline, in this particular one of its rôles, as a pituitary tropic hormone, or perhaps as adrenocorticotrophic-tropic hormone. The next event in the chain of events is, of course, the stimulation of the adrenal cortex by ACTH to produce its own hormones, including the celebrated and glamorous cortisone, and these in turn, as their titer rises in the blood when they reach the pituitary, shut down the latter's output of ACTH, and thus the hormonal circle is completed.

Long and McDermott claim a dual control of the secretion of ACTH by

the pituitary. That which results directly from stimulation of anterior lobe cells by adrenaline they call the "autonomic control"; that which results from a falling titer of cortical hormones in the blood they call the "metabolic." The concept is derived from the observation that in animals whose adrenal glands have been demedullated, and in animals in which destructive lesions have been produced in the thalamus and hypothalamus, the autonomic release of ACTH is abolished, whereas the metabolic response remains intact. It was further shown that homologous grafts of anterior pituitary tissue to the anterior chamber of the eye retain their ability to secrete ACTH both spontaneously and in response to adrenaline. Moreover, it was found that adrenaline injected directly into the anterior chamber of the eye containing the transplant caused a response even when given in very minute doses, too small to have any direct systemic effect. In neither the adrenal demedullated animals nor in those with diencephalic lesions could there be any reflex secretion of adrenaline, because in the former the gland which makes that hormone had been removed, and in the latter the reflex pathway had been interrupted. The transplanted anterior pituitary, however, subject only to hormonal stimulation, was able to respond either to administered adrenaline or spontaneously, under the control, presumably, of the blood titer of cortical hormones. These observations, which support a dual control theory with respect to adrenocortical functions, interest me greatly, and I would dearly like to know whether similar dual control exists in the case of other glands. Indeed, is dual control a usual organizational pattern of the endocrine system? and, if so, what are the other tropic-tropic hormones involved? Is adrenaline tropic-tropic to all the peripheral glands, or are there others? If there are others, are they derived from the adrenal medulla, the posterior pituitary, or elsewhere? Indeed, we would like to know what rôle in the overall outflow from the nervous system to the endocrine system is played by the posterior-pituitary. Certainly its hormone or hormones have widespread effects on blood sugar, on blood pressure, on the uterus, antidiuretic, etc., but are any of these mediated through the anterior pituitary or peripheral endocrines? These are all fundamentally important questions, but I do not believe that, at the moment, any of them can be answered. The elucidation of the adrenocortical pathway got ahead of that of others, because of the great ease with which adrenocortical activity can be tested for by means of the eosinopenic response. No equally convenient and rapid assays for TTH and GTH have yet been devised. One can make eosinophil counts as often as one likes; there is nothing to parallel this for the other tropic hormones. In the case of the thyroid there is some pertinent evidence, but it is hardly conclusive. Salter, for example, cites evidence that the blood iodine level rises after the administration of adrenaline, which fact would at least be consistent with a thyrotropic-tropic action of adrenaline, and Uotila has obtained results supporting a dual control for thyrotropic activity of the anterior lobe analogous to Long's for adrenocorticotropic. Uotila found that hyperplasia of the thyroid which follows exposure to cold fails to take

place if the pituitary stalk is cut, but that control of thyrotropic activity is effected by blood thyroxine level whether the stalk is cut or not.

I suppose by now you will feel entitled to an apology for terminology. Para-endocrine—that is to say, beside the endocrine—seems to me fair enough, but what of tropic-tropic? Can you bear with that? You may say, why “tropic” at all—why not “trophic”? Both these suffixes are in common use. What do they signify? Tropic is derived from τροπή, meaning turn—perhaps, turn toward. Trophic, from τροφικός, clearly carries the implication of something having to do with nutrition. It seems to me that to imply a nutritional quality to the impingement of a pituitary hormone upon its end-organ is to be more specific than existing knowledge justifies. “Tropic,” meaning turned toward, or “aimed at,” commits us to far less and therefore, in our ignorance, seems a more suitable term. Thyrotropic can be taken to mean aimed at the thyroid. Of course all hormones are aimed at some target; therefore, one might say all are tropic, and that the suffix is superfluous. It is convenient, however, when the target of one hormone when hit discharges another, to use the suffix tropic to define the former. Also, when a target is hit by a hormone and thereupon discharges a second hormone which hits a second target which discharges a third hormone, it seems to me reasonable to apply to the first hormone of the series the term tropic-tropic.

And this discussion brings me to the subject of targets or end-organs, a little-known area of endocrine physiology, but quite as essential to a comprehensive understanding of the workings of the endocrine system as is a knowledge of the synapse or the myoneural junction to an understanding of the nervous system. My own work has dealt with the thyroid, therefore I will discuss the action of the thyrotropic and thyroid hormones upon their targets by way of illustration.

The target of the thyrotropic hormone is the parenchyma of the thyroid gland. What happens when this hormone hits this target? There is available a certain amount of evidence bearing on this question, and it will be easiest to interpret it if we think in terms of the known functions of the thyroid gland. These all have to do with the manufacture of its hormone and may be identified as follows:

1. A mechanism for trapping iodide from the blood stream.
2. Synthesis of thyroxine. This involves iodination of tyrosine to diiodotyrosine and the coupling of two molecules of the latter to form thyroxine, all these reactions taking place within the chain molecule of thyroid protein-thyroglobulin.
3. Storage of hormone as thyroglobulin within the thyroid follicles.
4. Discharge of hormone to the body.

Study of the action of TTH on these functions has been facilitated by the fact that we now have drugs capable of divorcing these several thyroid functions. Potassium sulfocyanate, for example, blocks the trapping mechanism.

Thiouracil and its relations, on the other hand block the synthetic mechanism. TTH probably promotes all the functions of the thyroid but, when part is blocked, will accelerate the unblocked. Thus the gland blocked with thiouracil will still trap iodine when TTH is administered. It will also liberate hormone which, in view of the fact that the synthetic mechanism is blocked, must mean that TTH promotes the breakdown of stored thyroglobulin. The releasing of hormone may be the earliest effect of TTH on the thyroid. The work of De Robertis suggests that it is due to almost immediate activation of the proteolytic enzyme system of the thyroid, which brings about a reduction in the molecular size of stored protein and permits thyroxine-containing fractions to escape to the circulation. Hypertrophy and hyperplasia of thyroid parenchyma then follow with increased trapping of iodine and, finally, 48 hours or more after injection of TTH, increased synthesis of hormone.

In brief, these are the things TTH does to the thyroid gland. Now the question becomes, What does the thyroid do to TTH in the process? Rawson and his collaborators have shown that when TTH acts on the thyroid it disappears. This disappearance, however, is not due to destruction, because hormonal activity can be restored by heat or by certain mild reducing agents. The hormone is inactivated only, and remains capable of reactivation. It can be found in the urine in its inactivated form and, under certain circumstances, also in its active form.

The question of whether TTH has any specific targets, or end-organs, other than the thyroid cells, is important. When Rawson studied inactivation of TTH by thyroid tissue, he also made observations on other tissues, and found that both lymph node tissue and thymus caused partial inactivation. Adrenal, kidney, ovary, pancreas, parathyroid, testis, spleen and stomach mucosa caused none. Interpretation of these findings is not possible. All that can be said is that thymus and lymph node tissue do something to TTH. What, if anything, TTH does to them is not known. However, the suggestion is strong that these tissues are in some way targets for TTH. Somewhat stronger evidence connects TTH with the orbits. For some years now this hormone has been believed connected in some way with the ophthalmopathy of Graves' disease. At least it has been found experimentally that anterior pituitary extracts rich in thyrotropic principle cause marked exophthalmos in animals. This is accompanied in the orbit by edema and the laying down of connective tissue cellular elements, lymphocytes, macrophages and fibroblasts. This is a picture similar to that seen in humans with Graves' disease. Administration of TTH to animals releases fat from normal fat depots throughout the body, with deposition in skeletal muscles and particularly the muscles of the orbit. Also, blood fat rises and fat is laid down in the liver. These events occur in the thyroidectomized animal as well as in the intact, and are therefore not mediated through the thyroid gland. One may say, therefore, that areolar tissue may be included in the list of targets of the thyrotropic hormone.

The other hormone involved in the pituitary-thyroid axis is thyroid hormone. How does that one impinge on its end-organs; also, what are its end-organs? Presumably all cells in the body are targets or end-organs to the thyroid hormone, and its action on them is to stimulate their metabolic processes. This is a well known fact. However, in two special instances thyroid hormone inhibits its end-organs. As already mentioned, it inhibits the anterior pituitary in its thyrotropic function, and it inhibits the thyroid gland itself. When we come to the problem of the mechanism whereby the thyroid hormone exerts its action on its target we can find very little pertinent information. Presumably, thyroxine diffuses into the cell; at least, Professor Fritz Lipmann informs me that he finds it within cells in about the same concentration as in the serum, and distributed fairly evenly throughout the various elements of the cell. But how it exerts its action on the enzyme systems of the cell, and what happens to it in the process, remain to be elucidated.

Let us now turn again to the working of the endocrine system as a whole. One way of studying the nature of an integrating mechanism is to throw it out of gear at various points and observe what then happens. In the case of the endocrine system we can ablate portions of the system; we can administer hormones and, quite as important, we can investigate nature's endocrine disintegrations, namely, endocrine disease. It was from the last mentioned method, of course, that the first knowledge of the endocrine system was obtained.

There was a time when it was believed that by removing a single endocrine gland, or by giving a single pure hormone, one could isolate the action of one gland from the rest. But this is obviously not so. In a system made of infinitely interrelated mechanisms, as is the animal body, or at least the bodies of higher animals, one cannot alter any one part of the mechanism without altering the rest, for the rest must adjust to the disturbed part in order that commotion in the whole be kept at a minimum. Those physicians and surgeons who deal with a very restricted part of the body would do well from time to time to ponder these truths.

I will mention a few items which may illustrate what I mean. Aside from Addison's early recognition of the consequence of destruction of the adrenals, the important early endocrinology had to do with the thyroid. The connection of the thyroid with the clinical picture of myxedema, the discovery that feeding thyroid would remove this picture, seemed to tell most, or all, of the story about this particular endocrine organ. The rôle of the pituitary in thyroid function was not at all suspected, even though back in 1851 a French physician, Niépce, had made the important observation that the pituitary is hypertrophied in cretins. The significance of Niépce's work was not apparent until years after, when TTH had made its appearance on the medical scene.

It was back in 1889 that von Mering and Minkowski showed that pancreatectomy caused diabetes mellitus in dogs. In 1922 Banting and Best

obtained insulin from the pancreas, which relieved it. The situation in diabetes, however, is not as simple as that of the thyroid and myxedema; in fact, it is very complicated. In 1931 Houssay and Biasotti found that hypophysectomy prevents or ameliorates the diabetes caused by pancreatectomy, and from this emerged the concept of a diabetogenic hormone of the anterior pituitary which directly antagonizes insulin. A present opinion is that this hormone is identical with the growth hormone of the anterior lobe, or somatotropin. In 1935 Long and Lukens brought the adrenal cortex into the picture by discovering that adrenalectomy also ameliorates pancreatic diabetes. The hormone of the adrenal cortex of the 11-oxysteroid type, popularly known as cortisone, inhibits the oxidation of carbohydrate and, so Ingle has shown, causes violent aggravation of pancreatic diabetes and great resistance to insulin. The amelioration of pancreatic diabetes following adrenalectomy is believed to be due to the removal from the situation of the cortical diabetogenic hormone, cortisone. The diabetes of Cushing's syndrome is the result of the excessive production of diabetogenic cortisone by this hyperfunctioning cortex. It is insulin-resistant.

Thus at least three endocrines are brought into the diabetes picture, and we can bring in a fourth if we wish, namely, the thyroid. It has long been known that giving thyroid aggravates diabetes mellitus, and that when a diabetic person develops myxedema the diabetes is ameliorated. I have long supposed that these facts were to be explained on the basis of increased general (including carbohydrate) metabolism, by the thyroid hormone. Diabetes is aggravated by thyroid because the higher metabolism imposes a greater burden on the glucose burning mechanism, and removal of the thyroid gland diminishes it. But the thyroid may also play a more complex rôle. There is some evidence that hyperthyroidism also occasions hyperadrenocorticism. By what mechanism I do not know. The point is, however, that in addition to putting an extra strain on the sugar mechanism directly, hyperthyroidism may also call forth an increased discharge of diabetogenic cortical hormone. Houssay has found that giving thyroid to partially depancreatized dogs produces a type of diabetes indistinguishable from the usual form of pancreatic diabetes. When thyroid is withdrawn the diabetes disappears. He calls this "thyroid diabetes." If thyroid is continued long enough, an irreversible change may take place and a permanent diabetes result. This he calls "metathyroid diabetes."

The endocrine system is largely concerned in the now famous alarm reaction or adaptation syndrome of Selye. This investigator was bright enough to recognize that nearly any variety of violence or noxious stimulus, if sufficiently strong, sets off a chain reaction in the vertebrate animal which seemingly, at least in the healthy animal, is useful in preparing it to cope with the disturbing situation. In the diseased subject—the diabetic, for example, or the thyrotoxic—the alarm reaction may be highly injurious or even fatal by adding the extra burden of an adrenocortical diabetes to the preëxisting pancreatic or thyroid diabetes, thus throwing the patient in the former case

into diabetic acidosis and coma, and in the latter, into thyrotoxic crisis or so-called thyroid storm. Under such circumstances we may say that the endocrine integrating mechanism does not integrate—instead, it disintegrates the organism. Dr. Janet W. McArthur has made very extensive metabolic studies on a diabetic patient in the research ward of the Massachusetts General Hospital, and finds that even the withholding of insulin provokes an alarm reaction, with increased output of cortical hormones.

If, as the examples I have cited would seem to indicate, the endocrine glands are normally all in balance one with another, the effect of removing a part of them, or of giving an excess of the hormones of any of them, will obviously unbalance the system or throw it out of gear. I have wondered for many years, however, what would happen if the entire endocrine system could be ablated. This question came to my mind because of Cannon's experiments on the total ablation of the sympathico-adrenal system. Cats so operated on continued to live without apparent difficulty in the sheltered environment of the laboratory, but there were many adjustments they were quite unable to make, and they were totally unable to cope with the tough type of world in which a cat normally has to make its way. To conquer such an environment, the superstructure of a sympathetic nervous system is requisite.

And in the case of hormones, Long has made the point that they "do not initiate new patterns of cellular function; these are in the birthright of the cells themselves. All that any hormone does is either to facilitate or inhibit certain types of chemical transformation within the cells." If this concept is correct, one might speculate that as Cannon's cats got on in a limited way without their sympathetic nervous systems, so might animals deprived of their endocrine system make a shift to carry on the adaptive process in a limited way in a sheltered environment. But be that as it may, it is certain that, for normal living by the higher animal, an intact endocrine system is as requisite as an intact nervous system.

I would like to conclude with some comments on the present all-prevailing ACTH-cortisone furor. On all sides the time-honored principle of substitution therapy is being violated. In a subject whose thyroid is atrophic, we give a quantity of thyroid hormone which presumably approximates what his own thyroid gland would be making if it were capable of normal function. So doing restores the subject to a state approaching that of complete health. This is substitution therapy. When we give insulin in pancreatic diabetes we are also providing substitution therapy, although in this case, because the hormone is fast acting instead of slow like thyroid, it is more difficult to adjust the dose with great nicety to the precise need of the organism. Thyroid hormone provides specific substitution therapy only for athyreosis or myxedema, as it is usually called. Insulin provides it only for pancreatic diabetes. When large doses of cortisone (or ACTH to stimulate the secretion of cortisone) are given in a host of diseases, it is certainly not substitution therapy in the usual meaning of the word. Such

therapy is based on a totally different principle. It is not a matter of supplying in physiologic amounts a hormone which is lacking, it is rather one of giving a great excess of a hormone in the hope of thus neutralizing some injurious process which is causing the malady. We can quite properly regard myxedema as a deficiency disease—deficiency of thyroid hormone—but assuredly we cannot consider rheumatoid arthritis, asthma, lymphoma, or what have you, all the diseases which have been reported to have been benefited by these new hormones, as in any similar sense diseases simply due to deficiency of these hormones.

One can perhaps for a time neutralize the inroads of a morbid process by giving an excess of a hormone, as one can with a drug, but in so doing one cannot be said to have rebuilt a normal status, in the sense that one does by giving thyroid in myxedema. If a therapy produces a permanent change in a subject, then the subject must effect an adjustment to the therapy.

The situation may be likened to that in which one tries to bring to even keel a boat with a list to starboard by putting a load to port. Perhaps the boat is righted, but the original situation has not been restored. The boat is more heavily laden than it was and, if the load imposed is too heavy, the boat may sink!

I believe that is what will happen with the use of nonphysiologic dosage with ACTH and cortisone. There will be increasing numbers of untoward side effects. Already we are seeing a considerable number of these, and as the use of these hormones extends we will see more. According to the philosophy I have been trying to enunciate, such therapy, although productive of immediate symptomatic benefit, must be looked upon as, in its fundamental nature, disintegrating, and its use should be governed with that concept in mind. As I close I will leave with you that warning.

THE TREATMENT OF OBESITY WITH AN ANOREXIGENIC DRUG *

By ELLA ROBERTS, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

EXOGENOUS obesity is a constant problem in medical practice, and often a serious one. According to the Metropolitan Life Insurance Company,¹ persons only 15 to 24 per cent overweight have a death rate 44 per cent higher than normal, and for those 25 per cent or more overweight, the death rate shows an increase to 174 per cent. In certain conditions which are frequently characterized by obesity, the statistics are even more appalling. Overweight diabetics, compared with those of normal weight, for example, have a death rate of 257 per cent higher than normal.

While a fair number of overweight patients can and will lose weight by dietary limitation, a large proportion fail to cooperate and continue to overeat. It is now generally accepted that these failures often reflect some emotional difficulty which is satisfied by eating; this subject was thoroughly discussed by Williams² not long ago. Obviously, such persons require more than dietary instruction. Treatment by a psychiatrist may be indicated in some cases, but for the average patient the cost in time and money makes this prohibitive. The vast majority of overweight patients can, however, be led into a reducing program simply by understanding, sympathetic treatment, plus practical help and encouragement in the form of a safe means of appetite control.

Amphetamine sulfate has been widely used to curb appetite, and with good results. Its safety is now well established, but in the occasional patient there are some side effects which interdict its use. Most important of these is its interference with sleep, if the drug is taken late in the day. As such objectionable features result primarily from central nervous system stimulation, they could presumably be overcome by adding a mild sedative to the anti-appetite drug. A study of appetite control was therefore undertaken with such a combination of drugs.

MATERIAL

Subjects were from the clinics of the Woman's Hospital and from private practice. A total of 64 patients, four males and 60 females, was studied and placed on the régime. All the patients had been under supervision with dietary instruction for more than six months and had failed to lose weight. The age range was from 21 to 65 years. Ten were overweight diabetics who had been under treatment, including careful dietary instruction, for periods ranging from six months to six years. They had

* Received for publication July 7, 1949.

From the Department of Medicine, Woman's Hospital, Philadelphia, Pennsylvania.

remained markedly obese. Except for the diabetics, no patient showed any definite evidence of endocrine disturbance.

METHOD

Each patient was instructed to continue on the diet recommended to him before. This was adequate in all essentials except for total calories, which were restricted to 1,000 to 1,800 per day, depending on the sex, occupation and age of the individual. In addition, Dexamyl* was dispensed, to be taken as directed. Each Dexamyl tablet contains 5 mg. Dexedrine sulfate (d-Amphetamine sulfate, SKF) and 32.4 mg. Amytal (isoamyl-ethylbarbituric acid, Lilly). Patients were reexamined at two-week intervals for the first month and then at approximately monthly intervals.

DOSE

The optimal dose varied in different individuals. In general, those weighing less than 160 lbs. took one-half tablet three times a day; those

TABLE I
Average Weight Loss by Patients
(Grouped according to percentage overweight)

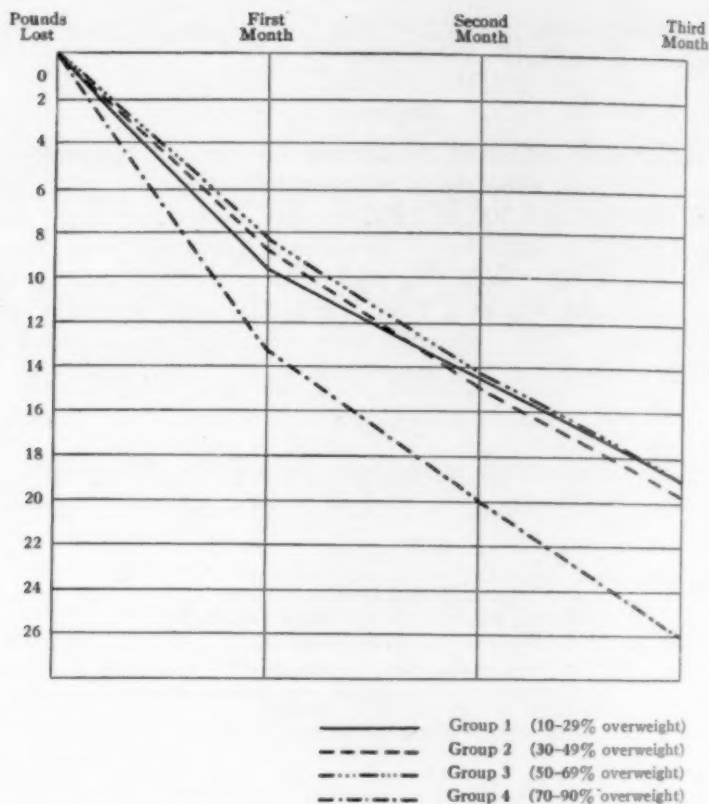
	Group 1	Group 2	Group 3	Group 4
Percentage overweight at start of treatment	10-29%	30-49%	50-69%	70-90%
Number of patients in group	18	24	9	8
Average weight loss at end of:				
One month	9.9	9.0	8.7	13.1
Two months	14.5	14.9	14.4	20.0
Three months	19.0	19.9	19.0	26.0

weighing 160 to 200 lbs., one tablet three times a day, and those over 200 lbs., one tablet four times a day. Best results were obtained by starting with one-half tablet three times a day and increasing the dose if necessary. In no case did the amount given exceed one tablet four times a day. Administration of the drug was timed to diminish hunger, usually at 11:00 a.m., 2:00 p.m. and 5:00 p.m., but the schedule varied with patients' times of rising, retiring and eating. If four doses a day were prescribed, the last one was timed to counteract the desire for an evening "snack."

RESULTS

Fifty-nine of the 64 subjects showed a satisfactory loss of weight throughout the three month study. Four patients failed to lose weight, although they did not gain while they were on this regimen. After two months' trial, however, they were considered failures, and are not included

* Supplied by Smith, Kline & French Laboratories, Philadelphia.



GRAPH I. Average weight loss of patients.

in the tables below. One additional patient was referred to the psychiatric clinic after a short trial. The data to be analyzed are, therefore, based on a total of the 59 patients who did lose weight.

Table 1 and graph 1 show the average weight loss of these 59 subjects over the three-month period. For purposes of analysis, the patients are grouped according to percentage above normal weight * for height, age and body build prior to treatment. In groups I, II and III, representing persons 10 to 69 per cent overweight, the average weight loss at the end of three months was 19.0 to 19.9 lbs. The average loss was somewhat higher—26.0 lbs.—in group IV, the patients who were more than 70 per cent overweight. These results would indicate that for most persons who are 10 to 70 per cent overweight, Dexamyl used in conjunction with a restricted diet might be expected to produce a loss of 9 to 10 lbs. in the first month, and between 4 and 6 lbs. a month thereafter. The larger loss of weight during the first month is usual in any reducing program. No tolerance to the anti-appetite effect of the drug was observed.

* According to Metropolitan Life Insurance Company standards.

TABLE II

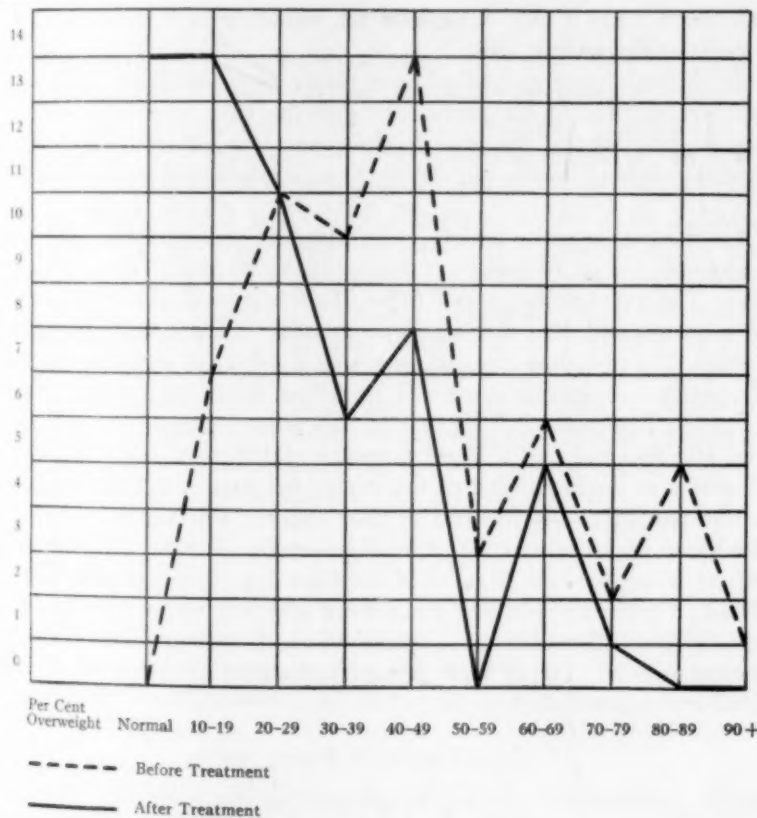
Weight Distribution of Patients

(Grouped according to per cent overweight at beginning and end of three months' treatment)

Percentage Overweight.....	Normal	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+	Total
Number of patients in each percentage group at start of treatment	—	7	11	10	14	3	6	2	5	1	59
Number of patients in each percentage group at end of three months	14	14	11	6	8	—	5	1	—	—	59

After three months' treatment, 14 (24 per cent) of the subjects attained normal weight, and 28 (48 per cent) were within 19 per cent of normal (table 2). The shift toward normal is readily apparent in graph form (graph 2).

Number of Patients



GRAPH II. Weight distribution of patients. (Grouped according to percentage overweight.)

SIDE REACTIONS

One patient reported vertigo from the medicine. She was placed on a placebo and reported a recurrence of vertigo. This patient was dropped from the study and later referred to the psychiatric clinic.

None of the other patients complained of any ill effects, although they were questioned carefully, particularly about "nervousness and sleeplessness." Several asked permission to take an additional dose at bedtime, admitting they had already done so. While they were advised to take 4 oz. of milk or tomato juice instead, they preferred the medicine and suffered no ill effects.

DIABETIC PATIENTS

Since excess weight is so hazardous and dietary control so important in diabetics, any agent which can safely control appetite in these patients deserves trial. For some reason, there is a rather vague belief among many physicians that the amphetamines are contraindicated in diabetes, but since they do not increase blood sugar,³ this idea seems to be unfounded. Actually, in our study of the 10 diabetics included in this series of overweight patients, there was, if any change at all, evidence of a decrease in blood sugar levels as the weight fell.

These diabetic patients had all been under observation for periods ranging from six months to six years. In general, they were mild cases: four required no insulin, and the dose in the others ranged from 12 to 40 units of Protamine (zinc) insulin per day. None of them had lost weight by diet alone.

When the anti-appetite tablets were added to their regimens, all the diabetics showed a loss of weight ranging from 10 to 26 lbs. within three months. The average loss was 7.6 lbs. the first month, 11.3 lbs. at the end of two months, and 16.7 lbs. in three months. These patients repeatedly commented, "I can follow my diet now that I don't get starving hungry."

The patients on insulin were able to reduce the dosage gradually as they lost weight. The most striking case in this respect was a woman of 50 who weighed 168 lbs. and had a blood pressure of 136 mm. Hg systolic and 84 mm. diastolic at the beginning of the study; her insulin dosage was 40 units Protamine per day. At the end of four months this patient weighed 151 lbs., the blood pressure was 120 mm. Hg systolic, 88 mm. diastolic, and she was getting along well on 18 units of insulin a day; the urine was sugar-free.

Although there are too few cases from which to draw any definite conclusions, the indications are that Dexamyl (which contains Dexedrine, one of the amphetamines), rather than being contraindicated, may be of definite value in overweight diabetics.

HYPERTENSIVE PATIENTS

Seven hypertensives referred by the cardiac clinic are also of some special interest. These patients had all been unable to lose weight. In view

Effect of Treatment on Weight and Blood Pressure of Hypertensives

Subject	Age	Weight		Blood Pressure	
		Before Treatment	After Treatment	Before Treatment	After Treatment
1	37	170	140	180/110	146/90
2	45	233	206	198/126	150/104
3	50	218	203	158/100	160/100
4	59	170	146	160/100	130/80
5	54	177	145	168/86	120/70
6	48	168	150	180/110	150/90
7	37	170	140	198/118	145/96

of the fact that Arnett⁴ failed to observe any deleterious effects in hypertensives when amphetamine sulfate was given in doses of 10 to 20 mg. a day, these subjects were included in the group treated with Dexamyl.

The average weight loss in this group was 25 lbs. In all cases but one, in which there was no change, the blood pressure was reduced at the end of the three-month treatment.

DISCUSSION

It is the author's opinion that Dexamyl is extremely valuable in reduction of exogenous obesity. Apparently it makes possible a lowered caloric intake without the overwhelming irritability which is apt to be associated with dieting. This information is volunteered repeatedly by the patients.

The encouragement of achieving weight loss, and the restricted eating habits established with the help of Dexamyl, enable many patients to diet successfully without drug treatment after a few months. This seems especially important, since Dexamyl contains a barbituric acid. The patients who reached normal weight have been followed for periods ranging from three to six months. They have all maintained normal weight, although the routine drug administration was withdrawn. In no case was there any evidence of habit formation to the drug. Five patients requested permission to keep a small supply on hand, explaining that it was useful when they were "upset" and wanted to overeat. They took about three to four doses a month and are now completely off all medication.

SUMMARY

1. A group of 64 obese patients who had been unable to lose weight, despite at least six months' dietary trial, was treated with Dexamyl (a combination of Dexedrine and Amytal) for appetite control.

2. Within three months, 59 of the patients reduced their weight considerably, bringing 14 of them to normal and 28 within 19 per cent of normal weight.

3. Ten diabetics included in the study all lost weight, and those on insulin were able to reduce the dosage, sometimes by more than 50 per cent.

4. The seven hypertensives treated with Dexamyl lost an average of 25 lbs.; in all cases but one, in which there was no change, the blood pressure was reduced.

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GASTRIC ACIDITY BEFORE AND AFTER DEVELOPMENT OF GASTRIC CANCER: ITS ETIOLOGIC, DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE *

By MANDRED W. COMFORT, M.D., F.A.C.P., Rochester, Minnesota

EVERYONE knows that in gastric cancer the mean gastric secretory activity is subnormal, but to what extent is it subnormal? What factors influence gastric acidity in gastric cancer? Does cancer develop in stomachs that already have subnormal gastric acidity, or does gastric secretory function become subnormal after cancer develops? What process is responsible for lowered gastric secretion? Finally, of what diagnostic and prognostic value is the degree of gastric secretory activity?

In the past two decades, many facts bearing on these questions have been recorded. These data will be summarized.

GASTRIC SECRETION IN NORMAL PERSONS

Survey of data from normal persons discloses certain basic facts about gastric secretion which must be considered in the study of gastric secretion in gastric cancer.

Gastric Acidity Varies Widely from Person to Person and with the Strength of Stimulant Used. Thus, with the Ewald meal,¹ the combined alcohol-histamine meal² and the histamine test,³ in the order named, the range of combined acidity in normal persons is, respectively, about 0 to 110, 0 to 130 and 0 to 150 units. Mean combined acidity also varies in the same order. Contrary to general impression, the percentage of achlorhydria apparently varies little, regardless of the strength of the stimulant used. The percentages are 10.8, 11.3 and 10.7 in men, and 13.8, 10.5 and 14.1 in women, respectively, with the Ewald meal, the alcohol-histamine meal and the histamine meal. The introduction of histamine apparently has not served to reduce significantly the percentage incidence of achlorhydria among normal persons.

Gastric Acidity Varies Not Only from Person to Person but in the Same Person from Time to Time. This we all have observed, and even histamine has not erased these variations. Schiff's⁴ study on gastric secretion, using histamine as a stimulant in a single normal subject over a period of four and a half years, has served to emphasize that "the human stomach may temporarily lose its ability, or may exhibit a marked decrease in its ability to secrete free hydrochloric acid for no definitely known reason and without change in the mucous membrane detectable on gastroscopic examination."

* Read at the meeting of the American Medical Association, Atlantic City, New Jersey, June 6 to 10, 1949. Received for publication December 9, 1949.

From the Division of Medicine of the Mayo Clinic, Rochester, Minnesota.

Secretion of Hydrochloric Acid Decreases with Increasing Years. It has been known for many years that achlorhydria is infrequent in children^{1, 5, 6, 7} and frequent in persons more than 50 years of age.^{8, 9, 10} Bloomfield and Keefer (1926, 1928),^{11, 12} employing the alcohol meal, plotted by decades the incidence of achlorhydria in 570 patients without organic disease, to show that achlorhydria increases in frequency from 7 per cent in the third decade to 40 per cent in the eighth decade. Vanzant and associates¹ (1932), using the Ewald meal (figure 1), and Polland⁸ (1933), using the histamine test, showed that a straight-line relationship between achlorhydria and age exists in normal persons.

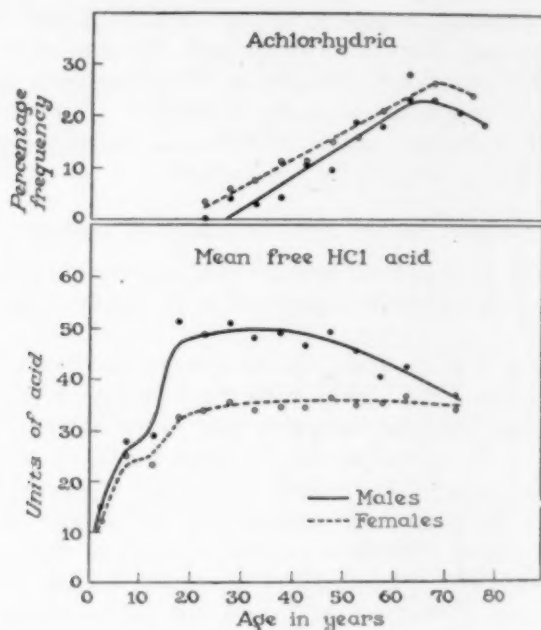


FIG. 1. Relationship of the incidence of achlorhydria and mean free acidity with age and sex in normal persons.

Secretion of Hydrochloric Acid Varies with Sex. Vanzant and associates (1932) showed not only that the incidence of achlorhydria increases in a straight-line relationship from youth to old age in both males and females but that achlorhydria is more frequent in normal females than in normal males (figure 1). Polland confirmed this, but Ruffin and Dick² failed to do so. Vanzant and associates also found (figure 1) that free gastric acidity appears to increase rapidly from childhood to the age of 20 years, when adult values are reached. At about the age of puberty the average value for boys begins to rise considerably above that for girls. Between the ages of 20 and 40 years the mean free acidity for men ranges

between 45 and 50 units and decreases thereafter to 30 to 35 units in the aged. The mean free acidity for women is approximately 35 units throughout adult life. It should be emphasized that these biologic relationships between gastric acidity and age and sex have been demonstrated whether the Ewald meal, the combined histamine-alcohol meal or the histamine test has been employed, and, consequently, regardless of the strength of the stimulant employed and of the resulting widely varying values for free acid.

Accurate appraisal of gastric secretion in gastric cancer requires comparison with normal standards based on age, sex and test substance employed.

GASTRIC ACIDITY IN GASTRIC CANCER

Ideas about gastric acidity in gastric cancer have altered markedly in the 70 years since von den Velden¹⁸ in his pioneer study (1879) found that the gastric contents in cases of gastrectasis due to cancer were achlorhydric. For a number of years it was thought that the gastric contents were always achlorhydric in cases of gastric cancer. Review of observations such as those by Miehle¹⁴ (1890), Oppeler¹⁵ (1895), Ewald¹⁶ (1902), Riegel¹⁷ (1903), Boas¹⁸ (1908), Cohnheim¹⁹ (1911), Einhorn²⁰ (1911), Smithies and Ochsner²¹ (1916), Osler²² (1919), and Hartman²³ (1922) discloses the gradual modification of this extreme concept, so that by the 1920's it was recognized that the percentage of achlorhydria is somewhere between 55 and 70 and that the concentration of free acid varies widely, sometimes even falling into the "hypersecretory" range.

In 1932, Vanzant, Alvarez, Eusterman, Dunn and Berkson¹ first provided adequate standards of normal, using data secured by the modified Ewald meal employed at the Mayo Clinic, by which the degree of abnormality could be measured. In 1933, Comfort and Vanzant,^{24, 25} employing this meal and these normal standards in the study of 805 gastric cancers, found that achlorhydria was approximately three times as frequent and mean free acidity was approximately 13 clinical units below the standards for normal persons of the same sex and age. Actually, the percentage of achlorhydria was 61.2 and mean free acidity 27.3 clinical units. Important for practical application of gastric acidity in gastric cancer for diagnosis, the range of free acidity extended from four to 86 clinical units, a range only slightly shorter than that in normal persons. There was not much difference in the acidity in the two groups in the lower part of the range; it was the higher acid values that tended to disappear in the presence of carcinoma of the stomach.

Ruffin and Dick,² employing the combined alcohol-histamine meal in 85 cases of gastric cancer, found the percentage of achlorhydria (56.5) to be almost identical but the mean free acidity (23 clinical units below the normal standard) considerably less than corresponding values obtained by Comfort and Vanzant. Pollard,³ using the histamine test, found the percentage of achlorhydria (69.6) to be greater than that obtained by Comfort and

Vanzant. Further studies with histamine will almost certainly disclose a secretory activity as good as that obtained with the Ewald meal.

FACTORS INFLUENCING GASTRIC ACIDITY IN GASTRIC CANCER

Sex. In normal persons there is a greater incidence of achlorhydria among women than among men,^{1,2} but in gastric cancer this relationship appears to be reversed. In 1933 Comfort and Vanzant found that free hydrochloric acid was absent from the gastric contents in about 62.8 per cent of the men and 55.9 per cent of the women with gastric cancer. Comparing the percentage of achlorhydria in normal men (18.4 per cent) and normal women (20.3 per cent) of the same age, achlorhydria was ap-

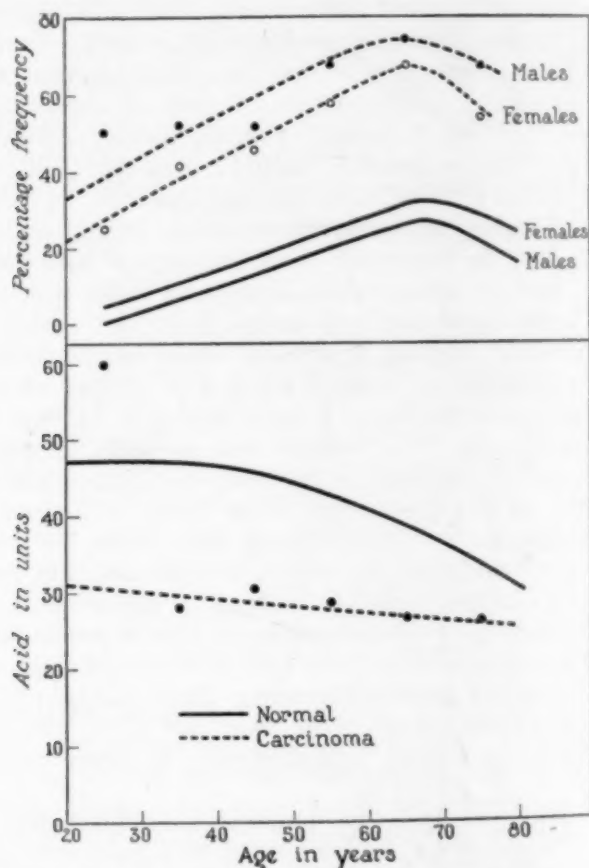


FIG. 2. Regression with age of percentage frequency of achlorhydria among persons with carcinoma of stomach contrasted with that of normal persons (upper). Regression with age of free acid among men with carcinoma of stomach contrasted with that in normal males (lower). (Reproduced with permission from Comfort, M. W., and Vanzant, F. R.: Gastric acidity in carcinoma of the stomach, *Am. J. Surg.* 26: 447-456, 1934.)

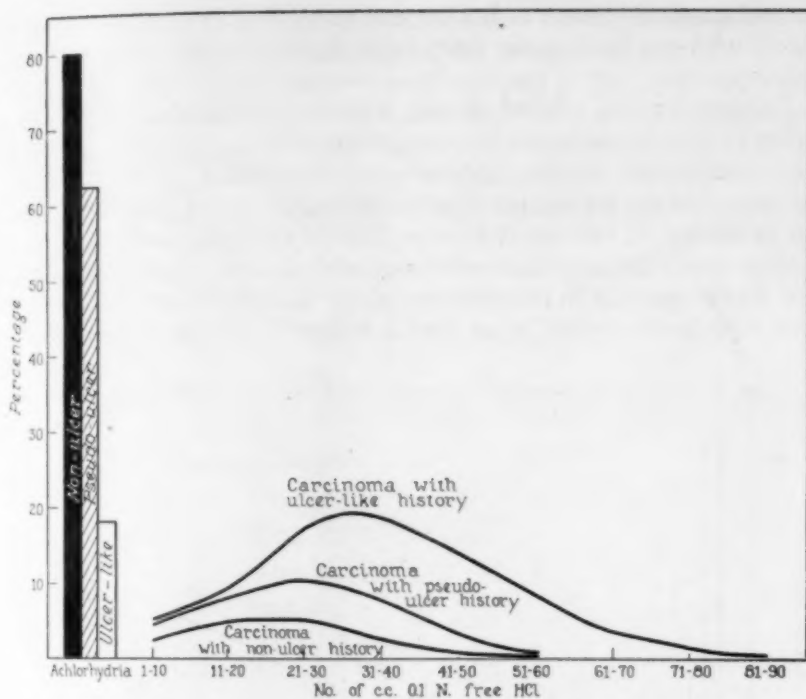


FIG. 3. Bar diagrams representing the percentage incidence of achlorhydria, and percentage distribution curves representing free acidity of patients with the three types of symptoms. (Reproduced with permission from Comfort, M. W., and Vanzant, F. R.: Gastric acidity in carcinoma of the stomach, *Am. J. Surg.* 26: 447-456, 1934.)

proximately three times as common among men and two and a half times as common among women with gastric cancer as among normal persons of the same sex.

In normal persons, mean free acidity is greater in men than in women; likewise in gastric cancer, mean free acidity apparently remains higher in men (28.2 units) than in women (24.6 units). However, the downward deviation from normal appeared to be greater in men (14 units) than in women (8.7 units). In gastric cancer a difference between secretion of free acid in men and women is measurable, just as in normal persons, but apparently the process responsible for the lowering of gastric acidity in gastric cancer has a decidedly greater depressant influence on the gastric acidity in men than in women.

Age. Mean gastric secretory activity falls steadily with age in patients with gastric cancer, just as in normal persons. The steady increase in the incidence of achlorhydria with advancing age seen in normal persons likewise occurs among patients with carcinoma (figure 2). The only difference is that the two curves for cancerous men and women are listed higher on the chart than those for normal men and women, owing to the fact that

the percentages are larger. It also was found that the free acidity of men falls off with age but that the rate of this decrease is not as rapid as it is in normal persons.

Symptomatology. Comfort and Vanzant^{24, 25} divided their cases according to symptomatology into three groups—ulcer, ulcer-like and non-ulcer—and constructed the bar diagram and distribution curves in figure 3. It is clear that the percentage of achlorhydria is much greater in the group with symptoms of the non-ulcer type than in the group with symptoms of the ulcer type. In fact, the incidence of achlorhydria is practically the same as in normal persons in the presence of an ulcer-like history, whereas it is about three times normal when such a history is absent (figure 4). It is

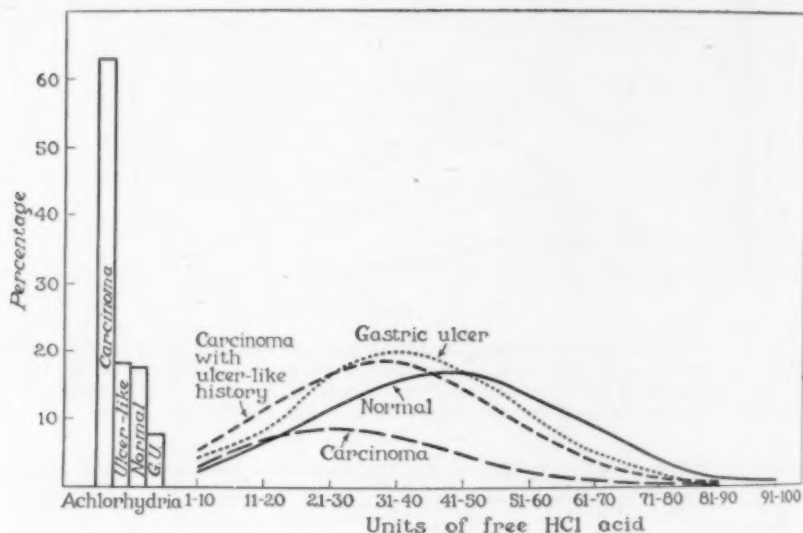


FIG. 4. Bar diagrams representing the percentages of achlorhydria, and percentage distribution curves representing gastric acidity of normal persons and of patients with benign gastric ulcer, of all patients with gastric cancer, and of those patients with gastric cancer who have ulcer-like symptoms. (Reproduced, with changes, from Comfort, M. W., and Vanzant, F. R.: Gastric acidity in carcinoma of the stomach, *Am. J. Surg.* 26: 447-456, 1934.)

also seen that the range of free acidity in the ulcer-like group was almost normal, whereas in the other two groups it was shortened about 40 per cent. In all three groups there was little difference in acidity in the lower ranges up to 20 units. The big difference came after this.

Resectability. Resectable lesions are associated with a higher mean secretory activity than is encountered in nonresectable lesions.^{24, 26, 26, 27, 28}

Size of Carcinoma. The greater the size of the cancer, the lower is the mean gastric secretory activity. Figure 5, which was constructed with data for the men in Comfort and Vanzant's series, shows that the incidence of achlorhydria increased rapidly with increasing size of the lesion, from 17.5

per cent with the smallest carcinomatous lesion to 93 per cent with the largest growths. As one would expect, the mean free hydrochloric acid was also appreciably higher with the smaller lesions. The same relationship was seen when women were studied and also when groups of both men and women with ulcer-like and non-ulcer symptoms were studied.

A most interesting observation was that with lesions less than 3 cm. in diameter the incidence of achlorhydria in the non-ulcer group was eight times

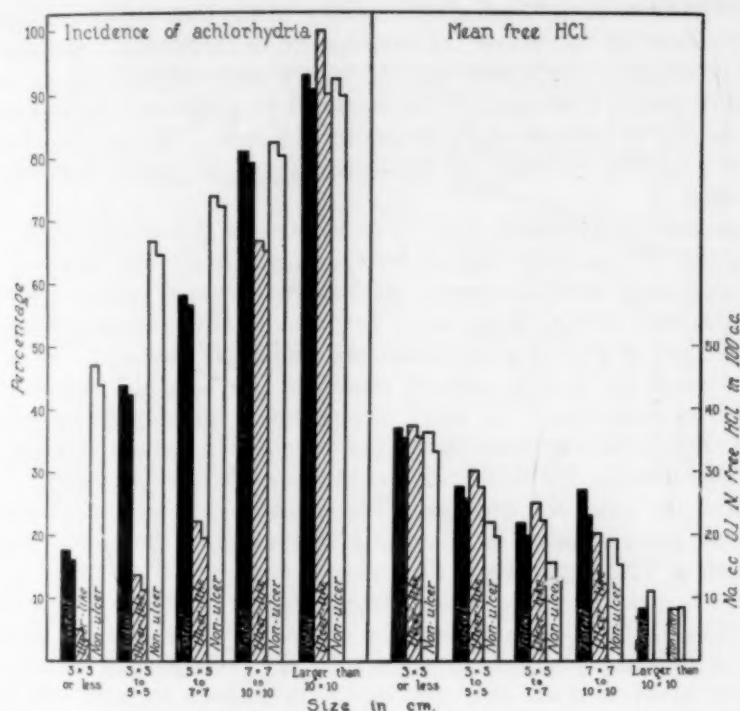


FIG. 5. Influence of size of lesion on percentage incidence of achlorhydria and on mean free hydrochloric acid in gastric carcinoma. Data for total group of men, as well as for ulcer-like and non-ulcer groups of men, are presented. Percentages of error are indicated by notching of each bar. (Reproduced with permission from Comfort, M. W., and Vanzant, F. R.: Gastric acidity in carcinoma of the stomach, *Am. J. Surg.* 26: 447-456, 1934.)

that observed in the ulcer-like group. Similar differences were found also with the larger lesions up to 7 cm. in diameter. The higher incidence of achlorhydria, even with the small lesion, suggests that in the non-ulcer group a carcinoma often arises in a nonacid stomach.

WHEN DOES THE REDUCTION IN GASTRIC ACIDITY TAKE PLACE?

Do persons in whom gastric cancer subsequently develops start life with a low mean secretory activity, or do they start life with a normal mean

secretory capacity that is partly lost before cancer develops? Or does some of the reduction take place after cancer develops?

Comfort, Butsch and Eusterman²⁹ (1937) and Comfort, Kelsey and Berkson³⁰ (1947) have provided data bearing on these questions. They studied cases of gastric cancer in which analyses of gastric contents were performed once or oftener two or more years before cancer was diagnosed. The interval of two years was chosen in order to be fairly certain that cancer was not present at the time of the initial test meal. The data were analyzed in three steps: first, gastric acidity at the time of the first analysis of gastric contents and before the development of carcinoma of the stomach; second, changes in secretory activity in the interval between the initial analysis of gastric contents and the diagnosis of gastric cancer, and, finally, gastric acidity at the time of the diagnosis of cancer. These data, especially those of Comfort, Kelsey and Berkson, appear to justify the following conclusions.

Mean Gastric Secretory Activity Is Subnormal Before Cancer Develops. Among the 277 patients studied by Comfort, Kelsey and Berkson³⁰ for whom analysis of gastric contents was done two or more years before cancer was diagnosed, 127 (45.8 per cent) had achlorhydic gastric contents, and 150 (54.2 per cent) had gastric contents containing free acid. In the 150 cases in which the gastric contents contained free acid, the mean free acid was 35.3 clinical units. In short, before cancer developed, the incidence of achlorhydria was greater by 24 per cent and the mean free acid was smaller by three clinical units than would be expected for a group of normal persons of the same sex and age. The mean gastric secretory activity of the precancerous stomach in this group was less than the normal standard at a mean of 11.2 years before cancer developed.

Mean Gastric Secretory Activity of the Patient in Whom Gastric Cancer Is Destined to Develop Is Subnormal at Each Decade of Life. Comfort, Kelsey and Berkson contrasted (figure 6) the percentage of patients who had achlorhydria and the mean free acidity of patients in each decade of life in these 277 cases of gastric cancer with similar data from groups of normal persons of the same sex and age. It is obvious that the percentage of achlorhydria in this group of precancerous persons is greater as early as the third decade and in each decade thereafter than in normal persons, and that the peak is reached in the fifth decade rather than in the seventh decade, as is the case among normal persons. Similarly, the mean acidity is lower for the precancerous group as early as the third decade, is lower for each decade than it is in the normal group, and is lower in the fifth, sixth and seventh decades than in the third and fourth decades. In short, mean gastric secretory activity of the precancerous group is subnormal as early as the third decade; it is subnormal in each decade, and more so in the latter years of life than in the early years.

Mean Gastric Secretory Activity of the Patient in Whom Gastric Cancer Is Destined to Develop Is Subnormal No Matter How Many Years Before

Gastric Cancer Develops Gastric Acidity Is Determined. Comfort, Kelsey and Berkson⁸⁰ plotted (figure 7) gastric acidity in relation to the interval in years between the initial analysis of gastric contents and the diagnosis of cancer, and against the acidity of groups of normal persons of the same sex and age. The contrast of data from the two groups is striking. The percentage of achlorhydria among precancerous patients is greater than the standard normal at each interval and is greater than 40 per cent at all intervals in years, at 10, 15, 20, and even 25 years before the development of cancer. Similarly, the mean free acidity is lower than normal even as

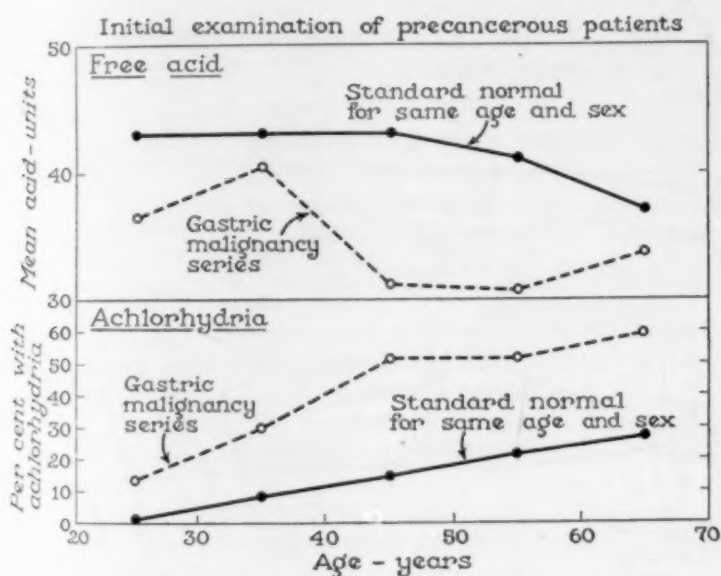


FIG. 6. Gastric acidity among persons in whom gastric cancer subsequently developed compared with gastric acidity among normal persons. At each age the percentage of persons with achlorhydria was higher, and for those who had acidity the mean acid was lower, than was true in a group of normal persons of the same age and sex as those in the experimental series. (Reproduced with permission from Comfort, M. W., Kelsey, M. P., and Berkson, J.: Gastric acidity before and after the development of carcinoma of the stomach, *J. Nat. Cancer Inst.* 7: 367-373, 1947.)

long as 10, 15 and 20 years before the development of cancer. Low mean gastric secretory activity of the precancerous patients precedes the development of cancer by as long as 20 to 25 years.

The Loss of Mean Gastric Secretory Activity Is Progressive. In this group of cases studied by Comfort, Kelsey and Berkson, between the time of the initial analysis of gastric contents and the diagnosis of cancer intervals of two to 39 years passed, the interval averaged 11.2 years, and the mean age of patients increased from 48.5 to 59.7 years. During this interval, and at the time of diagnosis of cancer, a further reduction in the gastric acidity had occurred. The percentage of patients who had achlorhydria had in-

creased from the initial 45.8 per cent to 68.8 per cent, or from the initial 24 per cent above the standard normal to 53 per cent above the standard normal. Similarly, the mean free acidity had decreased from an initial 35.3 units to 31.6 units, or from 3 to 5 per cent below the standard normal.

The Reduction in Gastric Secretory Activity Is Selective. Of the 150 patients studied by Comfort, Kelsey and Berkson whose stomachs contained free acid initially, 92 were given test meals at the time the diagnosis of cancer was made. Of the 92, achlorhydria had developed in 39 (42.4 per cent). The mean free acidity of gastric contents of the remaining 53 was 31.4 units,

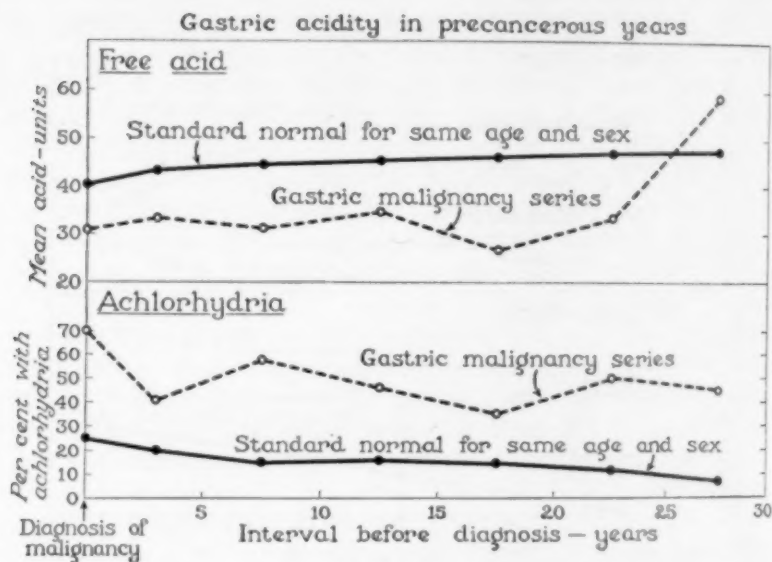


FIG. 7. Gastric acidity at progressively longer intervals before the time of diagnosis of gastric cancer. At all intervals recorded, and as long as 25 years prior to the diagnosis, the picture was one of low acidity as compared with normal. The percentage of achlorhydria was higher, and for those who had acidity the mean acid was lower, than for a group of normal persons of the same age and sex as those in the experimental series. (Reproduced with permission from Comfort, M. W., Kelsey, M. P., and Berkson, J.: Gastric acidity before and after the development of carcinoma of the stomach, *J. Nat. Cancer Inst.* 7: 367-373, 1947.)

lower by only 3.9 units than that of 150 patients with free acidity at the time of the initial test meal. When Comfort, Kelsey and Berkson grouped according to free acidity the 92 patients with free acidity at the time of the first analysis they found that the percentage of patients in whom achlorhydria developed was greatest among those with lower mean acidity and smallest among those with high mean acidity at the time of the initial analysis of gastric contents. The lower the initial free acid, the greater is the tendency for the gastric contents to become anacid. Conversely, the higher the initial mean free acid, the greater is the tendency for free acidity to be retained.

From these observations, it may be concluded that in these precancerous patients the process or processes responsible for the low mean gastric secretory activity had been active early in life and, in a considerable number of patients, many years before the development of cancer. The process had depressed mean gastric acidity in a greater percentage of patients in the later than in the early decades of life. It appears that the process responsible for the lowering of gastric acidity was a progressive one. This process seems to have been selective, for gastric acidity did not appreciably decrease in all cases.

WHAT IS RESPONSIBLE FOR SUBNORMAL GASTRIC ACIDITY IN THE PRECANCEROUS AND CANCEROUS STOMACH?

Five major hypotheses may be advanced in explanation of subnormal gastric acidity in the precancerous and cancerous stomach. An hypothesis based on the developmental aspects assumes that activity of this group of persons is subnormal at birth, remains so, and is the result of an inborn defect in the secretory mechanism. In support of this hypothesis is the occasional demonstration in the first years of life of achlorhydria and hypoacidity.^{1, 8, 9, 31}

A second hypothesis assumes that a degenerative process attacks the gastric mucosa of precancerous persons and that acid-cell atrophy, hypoacidity and achlorhydria appear with the passage of years.

A third hypothesis attributes the lowered secretory activity to destruction of the acid cells by chronic atrophic gastritis. That atrophic gastritis reduces gastric acidity cannot be doubted. Certainly mucosal atrophy does so in pernicious anemia, in which acid-secreting cells have almost completely disappeared regardless of the condition of the mucus-secreting cells.³² That atrophic gastritis may be partly responsible for the loss of gastric acidity in gastric cancer is supported by less convincing but highly suggestive evidence. First, chronic atrophic gastritis occurs in a high percentage of cases of gastric cancer.^{33, 34, 35, 36, 37, 38, 39} This has been observed gastroscopically and proved by microscopic examination of the mucosa of the cancerous stomach. Chronic atrophic gastritis appears to be present more frequently^{32, 34, 35} and in a more severe form^{35, 37} in gastric cancer than in any other condition.^{35, 36, 38, 40} Mean gastric secretory activity likewise is more subnormal in gastric cancer than in any other condition^{1, 41} except pernicious anemia. Second, gastric secretory activity decreases with age both in normal persons^{1, 2, 3, 41} and in patients with gastric cancer,^{24, 25} and the frequency of the occurrence of atrophic gastritis increases with advancing years.^{34, 38, 42} Third are the unconfirmed observations of Orator³⁶ and Baker⁴³ that acid-secreting cells are greatly reduced in number when achlorhydria exists and are more normal in number when free acid is secreted in cases of gastric cancer. Finally, it is of interest to note that if the loss of gastric acidity in gastric cancer is due to an anatomic change, atrophy of the acid-secreting

cells is the only known disease of the mucosa capable of producing a reduction which, as has been shown, occurs for the most part before cancer develops.

A fourth hypothesis attributes the lowering of gastric acidity to inhibitory substances capable of depressing gastric secretion. It has been shown definitely that the stomach may temporarily lose its ability, or may exhibit a marked decrease in its ability, to secrete free acid for no definitely known reason and with no change in the mucous membrane detectable on gastroscopic examination.⁴ No known stimulant, even histamine, is capable of stimulating the secretion of acid to the same degree at all times. The excessive production of inhibitory substances by the precancerous or cancerous stomach, such as that described by Brunschwig and his associates,^{45, 46, 47, 48} might conceivably play a rôle in producing subnormal acidity in the stomach with normal gastric mucosa both before and after the development of cancer.

Finally, gastric cancer itself decreases the already markedly subnormal mean secretory activity present before cancer develops. Actually, gastric acidity has been observed to fall in the cancerous stomach.^{49, 50, 51} It is possible that the cancer decreases secretory activity by producing gastritis, by destruction of the acid-secreting cells when the cancer is located in the fundus and in the body of the stomach, by increasing the amount of neutralizing fluid in the stomach, by exudation of serum from the ulcerated surface of the tumor, and by producing vitamin deficiency states capable of reducing gastric acidity.^{52, 53, 54} Logically, the quantity of hydrochloric acid secreted by the entire stomach should be quantitatively reduced in proportion to the percentage destruction of the total acid-secreting cells by the cancer. If destruction of acid-secreting cells by the gastric cancer plays an important rôle in reducing gastric acidity, a difference in the mean secretory activities of the stomach with cancers in the acid and nonacid secretory portions of the stomach should be measurable. This has not been demonstrated to date.^{23, 24, 25} At first glance, demonstration that the larger the cancer the lower is the mean secretory activity^{24, 25} supports the idea that the cancer may depress gastric secretion by destruction of the acid cells; but it is also possible that symptoms appear later and the cancer grows larger when achlorhydria is present before cancer develops than it does when mean free acidity is present. The finding by Comfort, Butsch and Eusterman in a small series of cases that the mean size of cancers developing in the presence of achlorhydria is greater than that of cancers developing in the stomach secreting acid, if confirmed, will support the latter interpretation.

IN WHAT SOIL DOES GASTRIC CANCER APPEAR TO DEVELOP?

Gastric secretory activity, therefore, is subnormal before cancer develops. It is subnormal in 80 per cent or more of patients with gastric cancers^{2, 3, 24, 25} and gastric polyps.⁵⁵ It is subnormal in all cases of pernicious anemia, the one disease in which evidence points to an incidence of gastric cancer and

gastric polyp greater than the general incidence.^{86, 87, 88} Chronic mucosal atrophy is present in all cases of pernicious anemia and in a high percentage of cases of gastric cancer, and the available evidence points to atrophy of the acid-secreting cells as the most likely cause of subnormal mean gastric acidity in the precancerous stomach. The soil in which a majority of gastric cancers develops, therefore, appears to be mucosa characterized by a markedly subnormal mean gastric secretory capacity and the seat of chronic atrophic gastritis. Those who support the thesis that chronic atrophic gastritis is the soil in which many gastric cancers develop may point to hyperplasia of the mucus-secreting cells as a fundamental reaction of the mucosa in bringing about repair after repeated injury to it, and advance the hypothesis that in some cases the process of repair, becoming disorganized and escaping the normal controlling influences, leads to formation of polyps and cancer. The more often repeated the injury and the greater the area of destruction and hyperplasia, the greater is the number of opportunities of the process to get out of hand and, consequently, the greater is the number of cancers occurring in diffusely diseased mucosa with markedly subnormal mean secretory activity. Such seems to be the case, at least, in pernicious anemia. Certainly, the hypothesis that atrophic gastritis is a precursor of gastric cancer is no more difficult of acceptance than that hyperkeratosis of the lip resulting from chronic trauma or that the mucosa of the colon diseased with ulcerative colitis predisposes, respectively, to formation of cancer of the lip and of the colon.

CLINICAL APPLICATION OF DATA ON GASTRIC ACIDITY IN GASTRIC CANCER

Achlorhydria as a Screening Device for the Early Detection of Gastric Cancer. Frequent roentgenologic examination of the stomach is the only method now available for early diagnosis of gastric cancer. Because frequent roentgenologic examination of the stomach of the entire population is far too great a problem for serious contemplation, Ivy⁸⁹ has proposed limitation of the number so examined to those in whom gastric cancer is most likely to develop. The screening device proposed by which such persons are to be found is based on age of the patient and gastric acidity. Because 90 per cent of gastric cancers occur in persons aged more than 40 years, because the gastric contents in approximately 60 per cent of cases of gastric cancer are achlorhydric, and because a major part of subnormality of gastric acidity apparently occurs before cancer develops, approximately 50 per cent of gastric cancers should develop in those persons aged more than 40 years who have achlorhydric gastric contents. The group is composed of seven to nine million persons, or that 15 to 20 per cent of the forty-seven million persons aged more than 40 years in the country today whose gastric contents are achlorhydric; it is in this group that one half of the forty thousand gastric cancers from which patients die yearly should develop.

The data on which this plan is based appear to leave little doubt that a

screening device based on age and gastric acidity will delimit a group in which the chance of gastric cancer developing is roughly eight to 10 times greater than in the general population. Once defined, the members of the group may be submitted to frequent roentgenologic examinations for the early detection of gastric cancer. Operation of such a program of early detection of gastric cancer might be considered successful if the percentages of resectable cases and of five-year survivals among the resectable cases are increased to 50. Development of this program of screening in early diagnosis of gastric cancer on the scale of present-day screening for pulmonary tuberculosis appears impractical, but each physician may operate a screening program among his own patients, choosing those with low gastric secretory activity for careful periodic clinical scrutiny and roentgenologic examination of the stomach. Patients with achlorhydria, especially those with diffuse atrophic gastritis, either idiopathic or in association with pernicious anemia, should be most carefully watched.

The Diagnostic Value of Gastric Acidity. Gastric acidity by itself will not enable one to distinguish with certainty between benign and malignant lesions of the stomach. When the Ewald meal is employed, free gastric acidity in normal persons ranges from 0 to around 100 units.¹ In gastric ulcer and in gastric cancer the range is not greatly different⁴¹ (figure 4). The overlapping of the three groups is so complete that absolute differentiation between benign and malignant gastric lesions is unlikely on the basis of gastric acidity alone. Ruffin and Dick² came to the same conclusion when the combined alcohol-histamine test was employed. Bloomfield and Pollard⁶⁰ expressed the belief that the histamine test meal, as practiced by them, might be of great value as a diagnostic procedure in cases in which the nature of a pyloric lesion is doubtful.

It must not be concluded from these data that the degree of gastric acidity has no practical value. On the contrary, given a small ulcerating gastric lesion, it may have considerable value in deciding for immediate operation or for a temporary trial of medical treatment. Because any gastric lesion more than 4 cm. in diameter is almost certainly cancerous, the question of malignancy or benignancy arises only when the lesion is small (less than 4 cm. in diameter), and only then is there need for employing the degree of gastric acidity as a diagnostic aid. Confining their study to lesions 4 cm. or less in diameter, Comfort and Butsch⁶¹ found that 64, 43, 16, 7 and 2 per cent of the lesions of this size were malignant, respectively, when gastric contents contained no free hydrochloric acid or free hydrochloric acid in concentrations of 1 to 19, 20 to 39, 40 to 59 and 60 or more clinical units. Gastric acidity, no matter what the concentration, did not assure benignancy; but the chance of malignancy was much greater when the gastric contents contained no free hydrochloric acid, or hydrochloric acid in low concentrations, than when free acid of a high degree was present.

From a practical standpoint, the physician should not prolong medical treatment of the small ulcerating gastric lesion much beyond three weeks

unless the lesion shows evidence of prompt healing by roentgenologic and gastroscopic examinations, symptoms disappear, and occult blood disappears from gastric contents and feces, regardless of the degree of gastric acidity, or, for that matter, regardless of any known factor, provided surgical treatment carrying a low hospital mortality rate is available, and the condition of the patient does not contraindicate surgical treatment. Medical treatment of an ulcerating gastric lesion with achlorhydria or low gastric acidity can scarcely be justified, because the chance of malignancy is great.

Achlorhydria associated with an apparent lesion of the duodenum may at times have a bearing on the problem of gastric cancer. Given achlorhydria and a roentgenologic report of a duodenal deformity, it is always well to remember that the deformity is rarely due to an active duodenal ulcer; it is more likely due to an old duodenal ulcer, healed long ago, to congenital deformity, to postcholecystectomic adhesions, or even to carcinoma of the pancreas. Most important, the lesion visualized by the roentgenologist may be, not duodenal, but gastric and a cancer.

It should be emphasized that the preceding remarks about the diagnostic value of gastric acidity in the presence of an intragastric lesion pertain to gastric acidity alone, and that the test meal gives other information of great value. The volume of gastric contents, and blood and retained food in the gastric contents, may be more important than the degree of acidity in arousing suspicion of an intrinsic gastric lesion.

The Prognostic Value of Gastric Acidity. Walters, Gray and Priestley²⁸ found that the percentage of five-year survivals of patients whose gastric contents did not contain acid or contained free acid in concentrations of 1 to 9, 10 to 19, 20 to 29, 30 to 39, 40 to 49 and 50 or more units were, respectively, 29.3, 19.7, 21.8, 27.4, 32.3, 39.1 and 42.1 per cent. It would appear from these data that the chances of five-year survival are best when gastric acidity is high, probably because such lesions produce symptoms earlier, causing the patient to present himself earlier for diagnosis.

SUMMARY AND CONCLUSIONS

Gastric acidity is subnormal in persons with gastric cancer. The percentage of achlorhydria is about three times as great and mean free acidity is about 13 clinical units less than the standard in normal persons of the same sex and age. However, the range of gastric acidity in gastric cancer is not greatly different from that of normal persons. The degree of subnormality of gastric acidity in gastric cancer varies with sex, age, resectability, symptomatology and size of the cancer.

A major part of subnormality of mean gastric secretory activity appears before gastric cancer develops. Mean gastric secretory activity of the pregastric cancer patient is subnormal regardless of the decade of life in which the test meal is performed and as long as 20 to 25 years before cancer develops. The lowering of mean secretory activity in gastric cancer is a progressive and selective one. Evidence now available tends to support

the hypothesis that atrophy of the gastric mucous membrane plays an important rôle in the depression of mean gastric secretory activity before the development of cancer, and the atrophic gastric mucosa is a soil in which gastric cancer frequently develops.

Values for free gastric acidity have a definite but limited clinical application in the gastric cancer problem. Their practical value as a screening mechanism in delimiting the group of persons in whom gastric cancer is most likely to develop awaits further study and application. They will not enable one to distinguish with certainty between benign and malignant gastric lesions, but in the management of small ulcerating gastric lesions the degree of free acidity of the gastric contents, without reference to other clinical, roentgenologic and laboratory data, gives valuable information about the relative chances of benignancy and malignancy and of the relative danger of even a temporary trial of medical treatment. As a prognostic device, the degree of free acidity in a case of gastric cancer may offer some encouragement to patients with high acidity, for the higher the secretory activity of the cancerous stomach the better the chances of five-year survival.

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MAINTENANCE DOSE AND TOXICITY OF DIGITOXIN *

By R. WAYNE MOODY, M.D., F.A.C.P., *Denver, Colorado*

THE availability of crystalline and weighable forms of digitalis has been a great step forward in the treatment of cardiac disease simply because dosage can now be determined with absolute accuracy. With this fact in mind, the majority of the patients in the Colorado General Hospital Out-patient Heart Clinic were placed on digitoxin over two years ago and have been kept on this drug from that time until the present. Digitoxin was chosen because its oral and intravenous dosage is essentially the same. Whether this advantage outweighs its disadvantages, particularly its long period of excretion, remains to be seen.

It was soon obvious that the effects on the cardiovascular system were no different and the toxic effects were the same as with other forms of digitalis, as will be further discussed in this paper. As a matter of fact, because of its high potency and comparative ease of use, we had more toxicity from digitoxin from inexperienced hands than from digitalis leaf.

In the following analysis all patients have been compensated and maintained at what we felt was an optimal level of digitalization for periods varying from a minimum of two months to a maximum of two years. None of the patients has decompensated while on the maintenance dose. In fact, most of the patients were digitalized to the point of slight symptoms, and then dosage was diminished to the disappearance of symptoms. A minimum period of two months was chosen because at least one patient developed toxicity only after two months on a constant daily dose of digitoxin. Because of this, no hospital patients were included in the study. Actually, one incentive for this report was the fact that many hospital patients discharged on a given dose came into the clinic two to six weeks later with symptoms or signs of digitalis intoxication. This again emphasizes the disadvantage of a very slowly cumulative and slowly excreted drug.

Although the number of patients in this study is not sufficient for detailed statistical analysis, it is sufficient as a basis for further study and, we feel, worth reporting. The maintenance dose of digitoxin is correlated to age, sex, weight and disease type in the report to follow, first in regard to the whole group of patients, then in regard to 62 cases of auricular fibrillation. The latter are reported in a group because it was felt that auricular fibrillation is the most accurate means of determining fairly exact optimal digitalization.

Correlation as to sex was of considerable interest. It is sometimes stated that the male requires more digitalis than the female. Ninety-five

* Received for publication November 18, 1949.

male patients required a mean digitoxin dose of 0.132 mg. per day. The per cent of males requiring over 0.1 mg. daily was 35.8. Further analysis of males by age revealed no wide difference in mean dose required. The age group from 50 to 59 required 0.141 mg., the age group from 60 to 69 required 0.137 mg. The age groups below 50 and above 70 required only slightly less. Therefore, there is actually only slight statistical difference with age.

Seventy-six female patients required a mean daily dose of 0.125 mg. Thirty-four per cent of the females required over 0.1 mg. per day. This is only 0.007 mg. less per day than males, and is certainly not of statistical significance. The females between 40 and 59 required slightly larger doses than those in younger and older age groups.

The obvious conclusion from the preceding is that sex makes little difference in the maintenance dose of digitoxin required.

Further analysis of age groups of males and females together was somewhat interesting in that, again, slight but probably definite differences were brought out by the following calculations: Only 26 per cent of patients over 70 required over 0.1 mg. per day; 37 per cent between 60 and 70 required over 0.1 mg. per day; 59.2 per cent between 50 and 60 required over 0.1 mg. per day; 39.9 per cent between 40 and 50 required over 0.1 mg. per day; 30 per cent between 30 and 40 required over 0.1 mg. per day; and 37 per cent below 30 required over 0.1 mg. per day. Again it would appear that the age group between 50 and 60 required slightly more digitoxin than the others.

Correlation as to weight was more interesting, as quite a definite trend could be shown in both males and females. However, patients under 100 pounds still occasionally required a 0.2 mg. daily dose, and patients over 200 pounds might still require only a 0.1 mg. daily dose. Figure 1 shows that there is a definite steady rise in maintenance dose from a weight of 160 pounds up. An average dosage of over 0.15 mg. per day was required for all patients over 180 pounds in weight. This was the only definitely obvious fact of value in regard to predicting maintenance dose.

Special study of 62 patients with auricular fibrillation gave us only the following facts of interest. Briefly stated, the mean maintenance dose was found to be 0.117 mg. per day, or slightly less than the entire group. This may be due to the tendency to push digitalization in a patient with a regular pulse, whereas in fibrillation one can be guided efficiently by the apical pulse rate and by the disappearance of pulse deficit. The average pulse rate of these 62 patients on maintenance digitoxin was 71 beats per minute, which we felt was an optimal degree of digitalization. Again there was no truly significant sex or age difference, although the age group from 50 to 60 required slightly larger dosage. In addition, correlation as to weight followed no such definite pattern as in the group as a whole, but since only four patients were included who weighed over 180 pounds no attempt was made to analyze the figures in detail.

Correlation of maintenance dose to disease type was of some interest. Of 164 patients, 57 were classified as coronary (arteriosclerosis of coronary arteries), 57 as rheumatic and 42 hypertensive.

The mean dosage required by the coronary group was 0.118 mg. per day. This group consisted mainly of older males—only eight females being included—some with conduction defects, bundle branch block, etc., who would be expected to require careful use of digitalis.

The rheumatic heart disease group required a mean dose of 0.128, but further analysis showed that combined aortic and mitral lesions in 29 patients required a mean dose of 0.137 mg. per day, whereas the patients with mitral lesions alone (28 in number) required a mean dose of 0.118 mg. per day. This difference, if significant, may be due to pushing digitalis in combined lesions, or possibly to difference in heart size, a study we should like to pursue at a later date.



FIG. 1.

Only eight patients with free single aortic insufficiency are included, so that the results are probably of little value. These patients (seven males and one female) were mostly luetic. Their mean dose was 0.168 mg. per day which, if significant, is a possible indication of the severity of the lesion and the attempt to push digitalis to its utmost. It is questioned whether any comment is justified on such a small number of patients.

Forty-two patients with essential hypertension were found to require a mean dose of 0.141 mg. per day. This increase, if significant, may be a result of two factors: the tendency of such patients to be overweight, and the fact that many of these patients fall in the 50 to 60 year age group. It therefore appears reasonable to conjecture that coronary heart disease should be digitalized and maintained somewhat more cautiously than other types.

In summary of this section of the paper, several facts are of interest. First, the average maintenance dose of digitoxin in our patients lies

between 0.1 and 0.15 mg. per day and is little influenced by sex or age, and only rather insignificantly by weight and disease type.

Second, in this very small series of cases, no patient required less than 0.05 mg. three times a week nor more than 0.2 mg. per day, although we are well aware of rare patients who require 0.3 mg. or even 0.4 mg. of digitoxin per day.

Third, as far as we can determine clinically digitoxin differs in no way in its beneficial effects from any other form of digitalis.

Fourth, once a proper maintenance dose is established for a given patient there is seldom any need to change it.

Fifth, due to the slow excretion of digitoxin, the tendency of inexperienced hands is to overdigitalize gradually over a period of a few weeks. This effect is easily overcome by frequent and careful observations of the patient.

The second section of this paper is devoted to the toxic effects and characteristics of digitoxin. The following study includes patients from the preceding group who exhibited toxicity at one time or another but who were relieved with reduction of the dose. All calculations on the group as a whole were made with the patients on maintenance nontoxic doses. The following studies are on 43 patients during the time that toxic effects were present.

This rather large number of 43 patients may be due to the fact that 0.2 mg. of purodigin was originally considered a comparably safe dose of digitoxin which could be given without too close supervision. This is not in keeping with our experience in this clinic. It is barely possible, however, that altitude (our clinic being at an elevation of over 5,000 feet) might play some part in digitoxin dosage, but we had always previously used dosages of digitalis leaf similar to those used elsewhere.

Only rarely has a dose of digitoxin over 0.2 mg. daily been used in the clinic. Two such patients are included in this study, and both were in the process of being digitalized. The one patient, a 70 year old male, received 0.4 mg. a day for one week, following which he complained of nausea, vomiting, headache and yellow vision. The second patient was given 0.3 mg. daily for 14 days, after which he exhibited complete A-V dissociation which disappeared shortly after withdrawal, although the P-R interval was still prolonged six days after discontinuance of the drug.

Twenty-seven patients showed evidence of toxicity on a dose of 0.2 mg. per day. There was no definite correlation of the symptoms with sex, age or weight. The patients were not the oldest patients in the clinic, as evidenced by the fact that the average age of all digitalized clinic patients was 61, whereas the average age of the toxic patients on the above dose was only 53. Also, weight distribution (average, 146 pounds) was little different from that of the group as a whole, whose average weight was 142 pounds. Males and females were almost exactly divided—13 females and 14 males—again illustrating that in our clinic there was little difference in digitoxin requirements in males and females.

Thirteen patients were toxic on dosages between 0.1 and 0.2 mg. of digitoxin per day. Ten of these 13 were on doses of 0.1 mg. daily. Two of these patients weighed 200 pounds, showing that a large individual can be toxic on a small dose. Again these patients were evenly divided between males and females, and the average weight was 146 pounds and average age 58 years.

Only one patient, a young woman of 25, evidenced toxicity on a dose of less than 0.1 mg. daily. She complained of rather severe nausea with occasional vomiting on a dosage of 0.1 mg. five days a week. She was relieved on a dosage of 0.1 mg. every other day. This was the smallest definitely toxic dose, although patients maintained on smaller doses have shown questionable evidence of toxicity.

Analysis showed that 23 patients complained of symptoms of digitalis toxicity and 23 patients showed signs of digitalis toxicity. Only three patients showed both simultaneously, which may be an indication of some carelessness in eliciting or recording symptoms. It may also indicate some decreased sensitivity to our red flags of digitalization, such as loss of appetite,

TABLE I

Nausea	17
Loss of appetite	5
Weakness	5
Vomiting	5
Yellow vision	3
Dizziness	3
Blurred vision	2
Diarrhea	1
Headache	1

nausea and vomiting. If this is true, and toxic signs do occur frequently without symptoms, then digitoxin must be watched even more closely and becomes a much less desirable drug. Further and more accurate study is needed to clarify these points.

The relative incidence of toxic symptoms is illustrated in table 1.

It is well known that loss of appetite is usually a precursor of nausea, but often patients are not asked about it and do not themselves complain until nausea appears. The above symptoms are, of course, no different from those due to any form of digitalis.

The signs of digitalis intoxication varied from mild to very severe. Twenty-three patients are included in the following synopsis.

Four patients are included whose electrocardiograms were interpreted as showing excess digitalis effect. These may or may not have been toxic. The remainder showed either single effects or combinations of effects, as indicated in table 2.

A quick review of the preceding shows that serious toxic effects occur readily on doses of 0.2 mg. digitoxin daily or less. Only one of the above patients received over that dosage. Sixteen of the 23 were on 0.2 mg. daily,

one was on 0.15 mg. daily, five were on 0.1 mg. daily, and one was on a dosage of 0.1 mg. five times a week. The latter exhibited a pulse rate of 54 as the only sign of toxicity.

Further study of toxicity on 0.1 mg. daily revealed only one serious effect, that is, a third degree heart block. This patient reverted to a first degree heart block on temporary discontinuance of digitoxin.

The patient with s-a block exhibited the phenomenon on a dose of 0.15 mg. per day, but showed a normal electrocardiogram on a dose of 0.1 mg. daily. The process could be reproduced.

Therefore, it may be concluded from this very small series that major toxic signs do not often appear on doses of 0.1 mg. or less, but appear rather frequently on doses of 0.2 mg. daily.

Of considerable interest and of no little importance was the notation of slowly developing toxic effects of digitoxin. This particular phase of the subject is thought to merit a slightly more complete description of the five following cases:

Illustrative of what we feel is the long period sometimes required for the development of toxicity is an 18 year old male with mitral stenosis and insufficiency and aortic stenosis and insufficiency. Following digitalization, he was maintained on a dosage of 0.2 mg. per day for a period of two

TABLE II

Bigeminal rhythm	6
Prolonged P-R interval	6
Numerous premature contractions	5
Pulse rate under 50	4
Pulse rate between 50 and 60 (in addition to other toxicity)	3
Complete heart block	2
Complete heart block with A-V nodal rhythm	2
Sino auricular block	1

months before he complained of nausea and vomiting. His pulse on this dose was 64 beats per minute. On 0.1 mg. per day, compensation was maintained, symptoms disappeared and his pulse averaged 74 beats per minute.

Similarly, a 75 year old male with coronary heart disease was given 1.2 mg. to start, then 0.2 mg. for five days, then 0.1 mg. daily for two weeks before his pulse fell to 54 beats per minute and he complained of marked weakness. Symptoms were relieved on only slight reduction, to 0.1 mg. six times a week, and the pulse rate rose to 80 beats per minute.

Another illustrative patient, a 68 year old woman with coronary heart disease took 0.2 mg. daily for 27 days until her pulse fell to 48 beats per minute and the electrocardiogram showed excessive digitalis effect.

Of even more interest are the following two cases: The first, a 33 year old female, on 0.2 mg. daily showed a gradual pulse fall over a period of

15 days from 96 beats per minute to 36 beats per minute; on 0.1 mg. daily the pulse rate was 88.

The second case, who previously had been on gr. 1.5 digitalis leaf, was put on 0.2 mg. digitoxin daily. After 28 days the pulse rate was 80 per minute, after 37 days the pulse rate was 55, after 58 days the pulse rate was 50 per minute, with occasional premature contractions and marked digitalis effect on the electrocardiogram. Placed on 0.1 mg. digitoxin the patient was well maintained and the pulse rate ran between 60 and 75 beats per minute, and the electrocardiogram showed moderate digitalis effect.

From the above we conclude that digitoxin may require as long as two months in an occasional patient before toxic symptoms appear.

We would like to reemphasize two conclusions from the preceding: First, even if our histories are taken with reasonable accuracy, serious signs of digitalis intoxication without marked symptoms may occur while taking digitoxin. The same is true, but possibly in a lesser degree, of any form of digitalis. This idea needs further clarification. Second, occasionally only slight reduction of dosage is required to relieve toxic symptoms or signs.

It is also worth mentioning that toxic symptoms from digitoxin may not completely disappear rapidly, as illustrated in the case of the 70 year old male with coronary heart disease on 0.3 mg. digitoxin daily for 14 days, whose P-R was still prolonged six days after discontinuance of the toxic dose.

Lastly, as a point of conjecture, it is possible that, by using too small a preliminary digitalizing dose and then too large a maintenance dose of a potent drug, we have produced some of the effects described in this paper. Only further experiment will determine if this is true.

In summary, and in correlation with the recent literature, we would weigh the advantages and disadvantages of digitoxin as follows:

The major advantage lies in a pure drug form which does not need bio-assay. This advantage is shared by digoxin and lanatoside C and cannot be minimized. Bio-assay of digitalis cannot be entirely satisfactory for two reasons, as pointed out in the therapeutic conference of the Johns Hopkins Hospital:¹ first, digitalis is a mixture of active principles which are not necessarily in constant relation; and second, the ratio of therapeutic action of animal to man is not necessarily the same for these different active principles. However, it must be pointed out that different preparations of digitoxin or digitaline may vary, and that there is need for more standardized means of preparation.²

The second advantage of digitoxin lies in its absorbability. Gold and others^{1, 2, 3} have stated that it is completely absorbed. Further, Gold states that it is rapidly absorbed with early effects, and that nausea and vomiting from local effect are rare.³ On the other hand, Evans, Dick, and Evans⁵ state that they found differences between the oral and intravenous dosage of digitoxin. They felt the oral digitalizing dose of 1.2 mg. to be too small,

whereas an intravenous dose of 1.2 to 1.5 mg. was adequate. De Graff⁶ states that the rate of absorption is not yet established.

In summarizing the disadvantages of digitoxin we would like to quote Master⁷ as follows: "I believe that digitoxin poisoning has now become so frequent an occurrence that it presents a real hazard." And, "Although Gold stated that his recommended dosage applied to only three-fourths of his series of patients, not only has his average dose been adopted indiscriminately for all patients, but worse still, much larger doses are prescribed."

Flaxman⁸ also reports an increased incidence of digitalis intoxication with the use of digitoxin, and Batterman and De Graff⁹ conclude that, until the pharmacology of digitoxin is somewhat better established, its use is safe only in the hands of a qualified cardiologist. It was our feeling during this study that the acceptance of a 0.2 mg. dose and the ease of use of digitoxin without appreciation of its dangers were the reasons responsible for the increased incidence of toxicity in our series.

A further major disadvantage of digitoxin is its long period of dissipation. The persistence of toxicity for as long as a week after discontinuance, shown in this article, has been commented upon by others.^{6,9}

A third disadvantage of digitoxin is its slow cumulative action. We found patients requiring up to eight weeks to develop full cumulative toxic effects. This same interval is described by Batterman and De Graff,⁹ and Master⁷ comments that digitoxin has the greatest cumulative action of all the glycosides. Further, in heart-lung preparations digitoxin is the hardest glycoside to wash out.¹ In humans, effects of a single dose may last for three weeks.

Nor is digitoxin the most rapid acting of the glycosides, as ouabain, digoxin and lanatoside C all have shorter latent periods.^{5, 6, 10, 11} Digitoxin may require 12 hours for maximum effect.¹

Others^{8,9} have commented on the lack of toxic symptoms before serious signs appeared, as we also observed. The absence of yellow vision is commented on by others,⁹ but in our series we encountered this symptom occasionally.

Finally, because possibly as many as one-fourth of the patients may be maintained on 0.05 mg. daily, such a tablet should be available.

CONCLUSION

1. The maintenance dose of digitoxin is between 0.05 mg. and 0.2 mg. per day. Only rarely is less or more required. A 0.05 mg. tablet should be available.
2. Patients frequently become toxic on a dosage of 0.2 mg. daily. All patients on such a dose should be observed frequently for a period of at least two months.
3. Digitoxin possesses the advantage of standardization by weight and of nearly complete absorption of an oral dose.

4. Digitoxin possesses the disadvantages of very slow dissipation. It probably is not a safe drug in inexperienced hands. Toxic effects may persist as long as a week after discontinuance.

5. Age, sex and weight have very little if any effect on the maintenance dose of digitoxin. Patients weighing over 180 pounds may require slightly larger dosage than those of less weight.

6. It appears probable that, with digitoxin toxic signs frequently appear before symptoms. If this is true, close supervision becomes even more imperative.

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THE VALUE OF FUNCTIONAL TESTS FOR THE DIAGNOSIS OF DISEASES OF THE PANCREAS*

By MARTIN M. NOTHMAN, M.D., *Boston, Massachusetts*

SINCE Whipple⁸¹ and Brunschwig⁸² have shown that carcinoma of the ampulla of Vater and carcinoma of the head of the pancreas can be extirpated with prolongation of life, resulting pancreatoduodenectomy has become a recognized procedure for the removal of these tumors. The ultimate surgical results will be influenced by awareness of these lesions on the part of the physician.

Furthermore, it has become increasingly evident that mild cases of acute pancreatitis are of common occurrence. Since Comfort¹⁸ in 1946 reported from the Mayo Clinic 89 cases of recurrent acute pancreatitis and described how the disease could be recognized, a surprisingly large number of these cases has been found in other clinics when the proper diagnostic procedures have been employed. In the past these cases of acute and recurrent pancreatitis have usually been mistaken for some form of biliary tract disease, such as biliary dyskinesia, postcholecystectomy syndrome, etc.

The importance of recognizing recurrent pancreatitis is increased since Doubilet and Mulholland^{14a} have shown in a series of 20 cases that prevention of further attacks could usually be affected by section of the sphincter of Oddi.

Hence the need of early diagnosis of recurrent pancreatitis and cancer of the pancreas is apparent.

The advance in the diagnosis of pancreatic disease is due to the employment of new functional tests. The laboratory approach has been along three general lines: (1) the study of the feces to determine the degree of digestion and of absorption and excretion of fat and nitrogen; (2) the determination of enzymes of pancreatic origin in the blood serum and urine, and (3) the estimation of the external secretion of the pancreas following pancreatic stimulation.

Diabetes mellitus and hyperinsulinism are not discussed here.

While the investigation of any pancreatic disorder need not start with an analysis of the feces, it is certainly incomplete without their thorough study. It is my experience from work in many clinics and laboratories that exact examination of feces is not done often enough. It is time consuming, and the technicians are loath to work with fecal material.

Careful investigation of the stools for undigested food very often gives the first suggestion of pancreatic insufficiency. By naked-eye examination the feces are bulky, light in color, often almost white, resembling aluminum

* Received for publication November 2, 1949.

From the Joseph H. Pratt Diagnostic Hospital, Medical Clinic, Boston Dispensary, Tufts College Medical School.

paint. Passage of butterlike masses is pathognomonic of pancreatic disease.

On microscopic examination the stools should be examined for fat, for muscle fibers and for starch granules. Large quantities of fat in the form of neutral fat, fatty acids and soaps (steatorrhea) may be seen. Neutral fats appear as yellowish flakes or droplets, fatty acids form flakes or needle-like crystals, and soaps occur as amorphous flakes or rounded masses as well as needle-like crystals. Addition of Sudan III will stain the neutral fat red and fatty acid flakes orange. Soaps will remain unstained. But if a drop of 30 per cent acetic acid is added and brought to the boiling point over a flame, fatty acids are liberated. These now will take up Sudan III and stain orange. When on microscopic examination the feces are stained with Sudan III without addition of acetic acid and boiling, even large quantities of fat may be overlooked if they consist mainly of soaps.

The occurrence of large numbers of undigested muscle fibers with longitudinal and transverse striations preserved (creatorrhea) may prove the deficient digestion of protein. By the addition of Lugol's solution, starch granules (amylorrhea) are stained blue, but their presence is of little diagnostic importance. It should be kept in mind that, even with frank pancreatic disease, muscle fibers may be broken down by the intestinal bacteria when the stools remain long enough in the intestine. In these cases creatorrhea may be missed.

The chemical studies of the feces should include the weight of the dried stools and their fat and nitrogen contents. Claude Bernard⁹ demonstrated in 1856 that absorption of fat is greatly decreased if the pancreatic ducts are completely blocked with paraffin. In 1890 Abelmänn,¹ under Minkowski's guidance, found that removal of a dog's pancreas caused a large decrease in the absorption of fat and protein from the intestinal tract. Pratt and his associates^{21, 22, 30, 40} have shown that in dogs there is great diminution in the absorption of nitrogen and fat when the pancreatic juice is excluded from the intestine by tying off all pancreatic ducts and interposing the omentum between the pancreas and the duodenum. When pancreatectomized dogs were fed with a neutral fat like olive oil, there was no absorption of fat. On the other hand, if a fatty acid like oleic acid is given to pancreatectomized dogs, a considerable absorption takes place. The absence of pancreatic secretion prevents the splitting of neutral fat which has to precede its absorption from the intestine. Large amounts of fatty acids may be found in the large intestine where the neutral fat is split by bacilli, but fat is not absorbed from the large intestine.^{33, 34, 35, 36}

The experimental work mentioned above is the basis for the diagnostic value of fat and nitrogen determinations in the feces in pancreatic disease. Balance studies of fat and nitrogen are time-consuming, but they are very important. The determination of the fecal lipids and nitrogen, without consideration of the fat and protein in the food, is of limited value and may be misleading.

As a test diet, we are now using a modification of the one recommended by Schmidt.⁴⁶ It is of similar composition but better adapted to the food habits of Americans. Like the original, it contains 105 gm. protein, 135 gm. fat and 180 gm. carbohydrate. It is given in six meals, as follows:

7:30 a.m.	1 egg fried with 5 gm. butter 50 c.c. orange juice 5 gm. sugar 60 gm. cream 1 slice of toast (20 gm.) 5 gm. butter	10:30 a.m.	1 slice of toast (20 gm.) 5 gm. butter 1 glass of whole milk
12:30 p.m.	60 gm. raw lean beef pattie 1 med. sized serving of mashed potato 5 gm. butter 1 glass of whole milk	3:00 p.m.	1 slice of bread (20 gm.) 5 gm. butter 1 egg custard
6:00 p.m.	60 gm. lean beef ground in sandwich of 1 slice of bread (20 gm.) 5 gm. butter 50 c.c. orange juice 1 glass of whole milk	8:30 p.m.	1 egg 5 gm. sugar 60 gm. cream 1 glass of whole milk 1 slice of toast (20 gm.) 5 gm. butter

The diet is given for three days. With the first meal, 0.3 gm. of carmine is taken within a capsule to mark off the stools. On the morning of the fourth day 1 gm. of charcoal is given with a breakfast consisting completely of milk. After the beginning of the test diet the stools are collected, from the first stool colored with carmine, until the first stool colored with charcoal. The first stool containing carmine is saved, the first stool containing charcoal is rejected. The charcoal is best given in the form of an emulsion. (Carbo vegetab. 15 gm., mucilag. gummi arab. 15 gm., aquae menthae pip. 60 c.c.) Of this 3 teaspoonfuls are taken.

In normal individuals, over 94 per cent of the fat and over 92 per cent of the nitrogen in the Schmidt diet are absorbed.⁸ Six per cent of fat and 8 per cent of nitrogen or less may be excreted with the feces. In complete obstructive jaundice due to gallstones, the amount of fat lost in the feces on the Schmidt diet averaged 26 per cent, but the absorption of nitrogen was within normal limits. In sprue the fecal nitrogen is essentially normal, whereas the loss of fat may amount to 45 per cent. In complete obstruction of the pancreatic ducts, about 60 per cent of the amount of fat and about 50 per cent of the amount of nitrogen from the diet have been recovered in the stools. While steatorrhea occurs in a variety of conditions, deficiency of

nitrogen absorption is almost invariably the result of pancreatic insufficiency.⁴¹

The weight of the dried stools may also give important information. In healthy persons, the average weight of the dried feces is approximately 54 gm. with the Schmidt diet (Bodansky⁸). With pancreatic juice absent from the intestine, the feces become bulky and the dried residue weighs more than that obtained in any other condition. It is Pratt's experience⁴¹ that in every instance in which the dried stools weighed more than 300 gm. there was complete obstruction of the pancreatic ducts.

Investigation of the carbohydrate metabolism may also have some diagnostic value in diseases of the external secretion of the pancreas. By far the most valuable laboratory procedure is the oral glucose tolerance test. The curve is flat in the active stage of sprue and normal or diabetic in steatorrhea of pancreatic origin.^{49, 50}

The second pathway in the laboratory approach to the recognition of pancreatic disease is the determination of enzymes of pancreatic origin in the blood serum and in the urine. These laboratory tests include the determination of diastase and lipase in the blood and of diastase in the urine. Determination of alkaline phosphatase in the blood may also be of some interest.

Serum diastase is believed to be derived primarily from the pancreas. But there is experimental and clinical evidence which indicates that not all of the diastase present in the blood is of pancreatic origin. The experimental basis for the use of the diastase test in pancreatic disease is the fact that tying of the pancreatic ducts is followed by a marked increase of serum diastase which, according to Pratt and his coworkers,¹⁹ may be persistent for weeks.

Our normal values for serum diastase are between 80 and 150 units per 100 c.c. of blood (Somogyi method).⁴⁸ It is of great diagnostic importance that in acute pancreatitis a high blood diastase is found within 12 to 24 hours of the onset of the acute symptoms. Shortly afterwards the diastase may fall to normal. In the most common form of pancreatic disease, the acute pancreatic edema, the increase of the serum diastase may even be more transient.¹⁸ The necessity for early and repeated determinations of the serum diastase, therefore, cannot be overemphasized. A sudden drop of serum diastase is not always a sign of improvement in the pancreatic inflammation. Extensive destruction of the pancreatic tissue may produce a similar reaction. If the first value obtained is moderately elevated, it is important to repeat the test at least once every day, as Pratt⁴⁴ has pointed out. If a rapid drop to normal occurs, the first value will obtain additional significance.

In the study of carcinoma of the pancreas and other chronic diseases of the gland, in the experience of most clinicians the serum diastase determination has been of much less value than the determination of the serum lipase.

An elevated level of diastase in the blood brings about an increase in urinary excretion of this enzyme. In the study of patients suspected of having pancreatic disease the determination of the concentration of diastase in the urine was a widely used procedure for many years. More recently the method has been employed less often, because examination of the blood serum for increased values of diastase and lipase has been found of greater diagnostic value.

The normal range of urinary diastase varies between 80 and 350 units per 100 c.c. in our laboratory, where the Somogyi ⁴⁸ method is used. Elevation of the urinary diastase is rare in cancer of the pancreas and in chronic pancreatitis, more frequent in recurrent pancreatitis. When present, it is always transitory and due to an intercurrent edema of the organ.

Dozzi ^{15, 16} determined the urinary diastase in different pathologic conditions. He examined patients with nephritis, diabetes, toxic thyroid disease, hepatic disease and pancreatic disease and found high and low figures in each group. Patients with pancreatic disease showed the highest figures, but low diastase values did not rule out pancreatic disease.

The urinary diastase test may be of great practical value under one condition—when acute pancreatitis or pancreatic edema is suspected despite a normal serum enzyme test. These cases may show an elevated urine diastase when the serum diastase is already back to normal. It is therefore suggested that a routine examination of the urine for diastase should be made without delay in every case of severe acute pain in the upper part of the abdomen.

In many respects, determination of the lipase in the serum should be more accurate in evaluating pancreatic disease than are studies on serum diastase, since, in our belief, serum lipase is definitely of pancreatic origin. This opinion has not been unchallenged.

Cherry and Crandall ⁹ found an olive oil splitting enzyme in relatively large amounts in the blood of dogs after ligation of the pancreatic ducts. The results have been confirmed in two dogs by Dozzi ^{16a} and in cats by Roe and Goldstein. ⁴⁵ But Popper and Sorter ³⁹ did not observe an increase of blood lipase after the operation. Referring to the experiments of these last-mentioned investigators, Bauman ⁴ believes that elevation of blood lipase after tying the pancreatic ducts has not yet been definitely proved. Through the work of Comfort and Osterberg ^{10, 11} and Johnson and Bockus, ²⁴ the experiments of Cherry and Crandall have become the basis for the clinical use of the serum lipase test in the diagnosis of pancreatic disease. Because of our interest in the evaluation of this test and its experimental foundation, Pratt, Benotti and I ³⁷ have studied the effect of the ligation of the pancreatic ducts and of pancreatectomy after duct ligation. We have found in 21 dogs that serum lipase rose in all to a high level.

The serum lipase is both pancreatic and extrapancreatic in origin. Its pancreatic origin is proved by the following facts: (1) rise of serum lipase after ligation of the pancreatic ducts; (2) decrease of the serum lipase after

total pancreatectomy, and (3) immediate drop of the serum lipase to almost zero after total pancreatectomy when the level for serum lipase previously has been raised by duct ligation. The recurrence of serum lipase two to three weeks or longer after total pancreatectomy proves that there exists also an extrapancreatic source for the enzyme. The rise of serum lipase is due to the absorption of the lipase into the blood stream after blocking the flow of pancreatic juice by tying the ducts. This is proved by making a pancreatic fistula after duct-ligation, as then the elevated serum lipase falls quickly to a normal level.

The most serious objection to the use of the lipase test for diagnostic purposes, particularly in the diagnosis of acute pancreatitis, has been the delay of 24 hours for incubation required by Cherry and Crandall's method.

Comfort¹¹ stated that values in excess of 1.5 c.c. measured with N/20 sodium hydroxide solution have pathologic significance. The material studied by Johnson and Bockus²⁴ indicated that some importance might be attached to any figure above 1.0 c.c. Values above 2.0 c.c. may be looked upon as definite evidence of pancreatic disease. According to our own experience, values above 1.0 c.c. have to be considered as pathologic.

In "acute pancreatitis" the serum lipase was elevated in 99 per cent of cases studied by Comfort,¹¹ while serum diastase was elevated in 88 per cent.^{10,11} But, as stated above, the enzyme determination must be performed early in the course of the disease.

In carcinoma of the pancreas, serum lipase may be found elevated especially if the test is repeated in serial fashion. A single estimation may be helpful but is seldom conclusive. Comfort and Osterberg^{10,11} found the serum lipase elevated in 28 out of 69 cases (40 per cent) of carcinoma of the pancreas, and in six out of nine cases (67 per cent) of carcinoma of the ampulla of Vater. Johnson and Bockus observed increased serum lipase in 16 of their 30 patients with primary carcinoma of the pancreas. In chronic pancreatitis, the serum lipase curve is indistinguishable from that of pancreatic malignancy.

In chronic relapsing pancreatitis, values for serum diastase or lipase or both were elevated in six out of eight cases during painful attacks, according to Comfort and his coworkers.¹³ Between painful seizures, serum diastase or lipase or both were elevated in three cases. We have found the serum lipase elevated in three, the serum diastase in four out of 16 cases of chronic relapsing pancreatitis during the quiescent period of the disease.

A third approach to the diagnosis of pancreatic disease through laboratory methods is the examination of the duodenal secretion following the use of pancreatic stimulants. Direct intubation of the duodenum was first accomplished by Gross and Einhorn in 1910. There were two major objections to the use of this method for the investigation of pancreatic function: dilution of the duodenal juice with gastric secretion, and the uncertainty of how much of the pancreatic secretion passed on down the intestine and how much was obtained through the duodenal tube. Most of the inaccuracy

of duodenal enzyme determinations was overcome by the principle of simultaneous aspiration of juice from both the stomach and duodenum, first employed by three physiologists, Lim, Matheson, and Schlapp²⁸ in Edinburgh. We use the double-lumen gastroduodenal tube introduced by the Swedish investigators Ågren and Lagerlöf,^{2,3} and employ continuous suction. In this way, most of the gastric juice and the greater part of the pancreatic juice are withdrawn through the two barrels of the tube.

Before the collection of the duodenal juice begins, the position of the tube should be ascertained with the aid of fluoroscopy. It must be at or near the ampulla of Vater. The help of the roentgenologist is of great importance.

TABLE I
Patient with Duodenal Ulcer (Age 38 yrs., weight 60 kg.)

Time	20' before In- jection of Secretin	0-10' after In- jection of Secretin	10-20' after In- jection of Secretin	20-40' after In- jection of Secretin	40-60' after In- jection of Secretin	Totals in 60 Min- utes	Normal Values
Amount of collected duodenal juice	21	33	29	53	49	164	75-400
Color	Dk. yellow	Lt. yellow	Colorless	Colorless	Colorless		
Consistency	Viscous	Viscous	Viscous	Viscous	Viscous		
Opacity	Opaque	Opaque	Clear	Opaque	Opaque		
Bicarb. mEq. (Bicarb. concentration)	12	97	128	125	105		Highest value for bicarb. conc.
Total alkalinity	2.5	32	37.2	66.3	51.5	187	75-130 60-275
Trypsin in 1 c.c.	7.1	7.1	2.1	4.9	4.2		
Trypsin in tot. amt.	149	234	60	259	205	758	150-750
Lipase in 1 c.c.	7.5	9.8	7.8	8.2	7.5		
Lipase tot. amt.	157.5	323.4	226.2	434.6	369.9	1,394	1,200-10,000
Diastase in 1 c.c.	120	177.5	130	487.5	152.5		
Diastase tot. amt.	2,520	5,857	3,770	28,537	7,472	42,936	12,000-142,000
Phosphatase 100 c.c.	9	21	5	3	3.4		
Phosphatase tot. amt.	1.9	6.9	1.5	1.6	1.7	11.7	
Bilirubin in mg. %	3.2	.4	0	0	0		
pH	6.8	8.3	8.9	8.9	8.8		

Most of our studies of pancreatic secretion have been performed with the secretin test. According to Bayliss and Starling,⁶ secretin is the hormone which stimulates the pancreatic cells to activity. Secretin is obtained by extracting the mucous membrane of the upper part of the jejunum of hogs. The substance is given intravenously in amounts proportionate to the weight of the individual. Duodenal juice is collected for 20 minutes before and three times (at 20-minute intervals) after secretin has been given. Un- toward symptoms have never occurred in our experience.

We determine the volume of the secreted juice, its concentration of bicarbonate, its total alkalinity, the concentration and total amounts of the diastase, lipase and trypsin, phosphatase, bilirubin and, occasionally, the hydrogen ion concentration. For the determination of diastase we use

Somogyi's method⁴⁸; for trypsin, Northrop's method³²; for lipase, a modification of Cherry and Crandall's method,³⁷ and for phosphatase, Bodansky's method.⁷ The concentration of bicarbonate is estimated by direct titration with one-tenth normal hydrochloric acid. We have performed the secretin test in almost 250 individuals.

When injected intravenously, secretin produces an abundant flow of pancreatic juice with a high bicarbonate content. The concentration of enzymes is sometimes less, sometimes higher than that of the spontaneous or fasting juice. But since the volume of juice is copious, the total output of enzymes is markedly increased.

TABLE II

Patient with Carcinoma of Pancreas Confirmed by Operation (Age 64 yrs., weight 67.5 kg.)

Time.....	20' before In- jection of Secretin	0-10' after In- jection of Secretin	10-20' after In- jection of Secretin	20-40' after In- jection of Secretin	40-60' after In- jection of Secretin	Totals in 60 Min- utes	Normal Values
Amount of collected duodenal juice	19	19	27	30	21	97	75-400
Color	Dk. yellow	Dk. yellow	Dk. yellow	Dk. yellow	Dk. yellow		
Consistency	Viscous	Viscous	Viscous	Viscous	Viscous		
Opacity	Opaque	Opaque	Opaque	Opaque	Opaque		
Bicarb. mEq. (Bicarb. concentration)	50	45	82.5	67.5	52.5		Highest value for bicarb. conc. 75-130
Total alkalinity	9.6	8.55	22.28	20.25	11.03	62.11	60-275
Trypsin in 1 c.c. Trypsin tot. amt.	1 19	0 0	0 0	0 0	0 0	0	150-750
Lipase in 1 c.c. Lipase tot. amt.	3.5 66.5	4.0 76	3.0 81	0 0	0 0	157	1,200-10,000
Diastase in 1 c.c. Diastase tot. amt.	65 123.5	65 123.5	0 0	0 0	0 0	123.5	12,000-142,000
Phosphatase 100 c.c. Phosphatase tot. amt.	15 2.85	18 3.42	14 3.78	12 3.6	10 2.1	12.9	
Bilirubin in mg. %	30.6	30	40.8	39	38.4		
pH							

Table 1 illustrates the effect of secretin in a case of duodenal ulcer without pancreatic involvement. The response is completely normal, as is shown when compared with the figures in the last column, which represent the normal range in about 150 cases. In this patient, the total amount of duodenal juice recovered in one hour after the injection of secretin is higher than 75 c.c., the lowest value which we still consider as normal. The bicarbonate concentration rises over 75 mEq.; the total alkalinity is higher than 60. The values for the total amount of trypsin, lipase and diastase are higher than 150, 1,200 and 12,000, respectively. The hydrogen ion concentration is between 8.3 and 8.9.

Tables 2 and 3 show the effect of secretin in two proved cases of carcinoma of the pancreas. In the first case, the total volume, the bicarbonate

concentration and the total alkalinity were still normal, but the values for the three enzymes were markedly reduced. Twenty minutes after injection of secretin the secretion of all enzymes ceased completely. In the second case, the total volume, the bicarbonate concentration, the total alkalinity and the total amount of the enzymes were all markedly reduced.

In the diagnosis of carcinoma of the head of the pancreas, the secretin test is a great aid. Reduction in volume of secretion, reduction of alkalinity of the pancreatic juice and decrease or absence of enzymes after stimulation with secretin are the characteristic changes of pancreatic secretion in cases with carcinoma of the gland.

TABLE III

Patient with Carcinoma of Pancreas Confirmed by Operation (Age 63 yrs., weight 72 kg.)

Time.....	20' before In- jection of Secretin	0-10' after In- jection of Secretin	10-20' after In- jection of Secretin	20-40' after In- jection of Secretin	40-60' after In- jection of Secretin	Totals in 60 Min- utes	Normal Values
Amount of collected duodenal juice	3.5	10	7	9	4	30	75-400
Color	Dk. yellow	Clear	Clear	Clear	Dk. yellow		
Consistency	Viscous	Viscous	Viscous	Viscous	Viscous		
Opacity	Opaque	Clear	Clear	Opaque	Opaque		
Bicarb. mEq. (Bicarb. concentration) ° Tot. alkalinity	18 .63	25 4.3		50 6.5		10.8	Highest value for bicarb. conc. 75-130 60-275
Trypsin in 1 c.c. Trypsin tot. amt.	Not done due to lack of material	3.4 57.8		4.8 62.8		120.2	150-750
Lipase in 1 c.c. Lipase tot. amt.	18 63	24 408		10 130		538	1,200-10,000
Diastase 1 c.c. Diastase tot. amt.	80 280	65 1,105		130 1,690		2,795	12,000-142,000
Phosphatase 100 c.c. Phosphatase tot. amt.		23 3.9		20.6 2.68		6.58	
Bilirubin in mg. %		0		0			
pH		8.4		8.8			

In those cases of carcinoma of the pancreas where the tumor is not localized in the head of the gland, no change in secretion may occur. In respect to the relative incidence of involvement of the head as compared with that of the body and tail, a large variation is reported in the literature. Duff,¹⁷ Kenney,²⁸ Hick and Mortimer,²³ and Silver and Lubliner⁴⁷ have found the carcinoma in the body or tail in 32 to 47 per cent of their cases, whereas D'Aunoy, Ogden and Halpert,¹⁴ Leven²⁷ and Grauer²⁰ have seen the tumor in that region in only 15 to 23 per cent. Lagerlöf,²⁸ Comfort¹² and Pollard and his coworkers³⁸ have described cases where the carcinoma of the pancreas was localized in the body of the organ and where there was a normal response to secretin. We have observed a similar case.

During the last two and a half years we have made the diagnosis of carcinoma of the pancreas in seven cases. Among the laboratory tests, the secretin test has proved to be the most reliable. Table 4 shows the result of the enzyme studies and the secretin test in these cases. In one case the secretin test was not done because the patient was too sick for its performance and died a few days after admission. Five other cases showed a markedly decreased response to secretin. The sixth patient had a normal response; on the operating table a carcinoma of the body of the pancreas was found. Serum lipase was elevated in only one case. The serum diastase was increased in the same patient. The serum diastase in the other cases was normal. Urine diastase was elevated in three cases. Among those was the patient with the carcinoma of the body of the pancreas who had shown a normal response to secretin.

We have also studied four cases with pancreatic lithiasis and one case with calcified pancreas. In all the secretin test yielded reduced amounts of fluid with a low concentration of all enzymes.

TABLE IV
Laboratory Tests in Cases of Carcinoma of Pancreas

Patient	Serum Lipase	Serum Diastase	Urine Diastase	Secretin Test
G. M.	4.86	1,296	1,675	Not done
M. C.	0.8	78	590	Diminished response
W. R.	0.5	115	1,190	Normal response
F. H.	0.6	90	250	Diminished response
M. L.	0.5	110	175	Diminished response
R. S.	0.5	120	250	Diminished response
E. B.	0.4	144	130	Diminished response

The secretin test was performed by Maddock, Farber and Schwachman²⁰ in normal infants and in others with celiac disease, malnutrition and pancreatic fibrosis. An increase in the volume of duodenal juice was noted after secretin injection in the healthy subjects, but no change occurred in patients with pancreatic fibrosis. In the cases of pancreatic fibrosis, duodenal aspiration yielded thick sticky material rather than the normal thin watery fluid. The values for trypsin were near zero. We have confirmed these results in 10 cases at the Boston Floating Hospital. They were examined for the purpose of differentiating idiopathic and pancreatogenic steatorrhea. In eight cases the secretin test was normal; in two cases with cystic fibrosis there was no response at all to secretin, and the values for trypsin were zero. Cystic fibrosis of the pancreas is not an uncommon disease. It has been found in 2 to 4.8 per cent of autopsies of infants and children.²⁰ The authors agree that the examination of the duodenal juice for pancreatic enzymes is the most reliable diagnostic aid. The response to secretin is even more reliable.

Pratt ⁴⁸ has observed two patients with transitory hypocholia pancreatica in which the volume, alkalinity and enzymes were reduced almost as greatly as in cases of carcinoma.

In acute pancreatic disease of slight or moderate severity, according to Ågren, Lagerlöf and Berglund,⁸ the secretin test reveals an isolated lowering of the diastase, the other values remaining within normal limits.

For the diagnosis of chronic pancreatitis and chronic relapsing pancreatitis, the secretin test is less valuable. If large parts of the gland are involved a lowering of both the amounts of bicarbonate and of enzymes may be found. The values are not so sharply reduced as in pancreatic carcinoma but they are low enough to suggest pancreatic disease. We have seen five cases which showed this kind of response to secretin, and these have been operated upon either with the tentative diagnosis of pancreatic carcinoma or because of the presence of gallstones. On the operating table the examination of the pancreas disclosed chronic pancreatitis.

In the last three years we have been particularly interested in the value of the secretin test in the diagnosis of cases in which the clinical evidence seemed to point to a diseased pancreas but in which the gland was subsequently found to be normal. The secretin test has been of great value in differentiating carcinoma of the extrahepatic bile ducts and carcinoma of the pancreas. The signs and symptoms are very much alike. Neither separately nor in combination are the clinical manifestations striking enough to permit the differential diagnosis. A thorough examination of the feces may be helpful in some cases. Under these circumstances the secretin test is an important diagnostic procedure. In painless obstructive jaundice, diminished total alkalinity and diminished pancreatic ferments support the diagnosis of carcinoma of the pancreas. Painless obstructive jaundice with normal total alkalinity and normal pancreatic ferments favors the diagnosis of carcinoma of the biliary tract.

We may add that we have in the secretin test a reliable aid to differentiate pancreatic steatorrhea and nontropical sprue. In pancreatic steatorrhea the enzymatic activity of the duodenal juice is low. After the injection of secretin there is little or no increase of the total volume and the total alkalinity, and slight if any increase of the total amount of enzymes. In sprue, the response of the pancreas to secretin is completely normal in that the duodenal juice shows increased volume, increased total alkalinity and an increase in the total amount of the enzymes.

Instead of secretin, parasympathomimetic drugs have been used to stimulate pancreatic secretion. Comfort and Osterberg¹² employed mecholyl and found the total alkalinity and volume lower and the concentration of enzymes higher than after secretin. I myself studied the influence of magnesium sulfate upon the composition of duodenal juice. I found the effect of magnesium sulfate similar to the effect of secretin but less marked. According to my own experience, the secretin test is more reliable than the test with mecholyl or magnesium sulfate for diagnostic purposes.

The different laboratory methods which may be helpful in the diagnosis of pancreatic disorders have been presented. One is often asked which is the most reliable. There is no uniform answer to this question. In the differential diagnosis of pancreatic and nonpancreatic steatorrhea, thorough studies of the fat and nitrogen absorption may be particularly useful. For the diagnosis of acute pancreatitis and pancreatic edema, and often for the diagnosis of malignant lesions of the pancreas, the determination of enzymes in the serum may be especially helpful, although our own experience with the lipase test in pancreatic carcinoma has been disappointing. In the diagnosis of chronic pancreatitis with recurring exacerbation, the determination of diastase in the blood and in the urine may be of particular value. And for the diagnosis of carcinoma of the pancreas and pancreatic lithiasis, the secretin test may be decisive. These tests should be evaluated together, since in most cases no single test can establish a diagnosis. The serum lipase may be normal at a time when the result of the secretin test is in favor of carcinoma of the pancreas, and in pancreatic edema the serum lipase may still be high when the serum diastase or urine diastase are normal. Therefore, enzyme studies and the secretin test and, in some cases, the determination of the absorption of fat and nitrogen by the chemical analysis of the feces are necessary for the exact diagnosis of pancreatic disorders. In all cases a careful gross and microscopic study of the stools should be made. The results should be used in conjunction with all available clinical data. Most often the diagnosis is missed because, as Pratt⁴⁴ expressed it, physicians forget that the patient has a pancreas.

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THE RESULTS OF SPLENECTOMY IN BANTI'S SYNDROME*

By ROBERT H. DURHAM, M.D., F.A.C.P., *Detroit, Michigan*

THE clinical concept of Banti's disease has undergone an evolutionary transition found in few other diseases. Concurrent with this changing knowledge, the original name Banti's disease has been supplanted by a succession of other terms. Osler was among the first to challenge Banti's original interpretations. After observing cases without any apparent hepatic involvement, Osler suggested that this type of case should more appropriately be called *splenic anemia*. This term has since become obsolete. *Banti's syndrome* later came into use as a general descriptive term and continues to be used by many clinicians. As the rôle of the spleen became better understood, with acceptable proof that splenomegaly is a secondary congestive phenomenon, a result of increased portal pressure, the term *fibro-congestive splenomegaly* was introduced. Other clinicians prefer to use a currently popular synonym, *congestive splenomegaly*.

None of these terms very accurately describes the variable clinical picture which may be encountered in this disease process. In the earlier stage of the pathologic derangement there may be found only a mild or moderate splenomegaly, leukopenia and anemia. During this period the term *congestive splenomegaly* seems applicable, since it emphasizes the most tangible pathologic change present. On the other hand, a term which emphasizes only the splenomegaly seems wholly inadequate in its terminology when there may also be present an advanced degree of Laennec's cirrhosis with hepatic insufficiency and ascites, an extensive collateral circulation with esophageal varices, and an altered function in the bone marrow with pancytopenia. Furthermore, the splenomegaly is generally considered to be a secondary feature, a sequela of the portal hypertension. This arbitrary grouping of the variable stages of the disease under such a categorical term has made a proper statistical evaluation of the results of splenectomy rather difficult.

The current concept of *Banti's syndrome* postulates the presence of an obstructive lesion involving either the splenic or portal vein or the intrahepatic venous system, and of sufficient degree to cause a portal hypertension and congestive splenomegaly.

The most common type of intrahepatic obstructive lesion is a Laennec's type of cirrhosis. Rarely, other types of lesions such as congenital narrowing of the intrahepatic portion of the portal vein may cause a similar clinical

* Presented at the Thirty-first Annual Session of the American College of Physicians, Boston, Massachusetts, April 19, 1950.

Received for publication December 6, 1950.

From the Department of Medicine, Division of General Medicine, Henry Ford Hospital, Detroit, Michigan.

picture. Aggregate statistics indicate that a Laennec's type of cirrhosis is present in approximately 70 per cent of cases of Banti's syndrome. Cirrhosis from infestation with *Schistosoma mansoni* has frequently been observed in other localities, but was not found in the 70 cases studied in this clinic. Other writers have emphasized that this type of cirrhosis is to be suspected when the portal pressure is high and the spleen is unusually large.¹ If the obstructive lesion is extrahepatic, the liver is usually uninvolved. By far the most common type of extrahepatic obstruction is a thrombosis of the splenic or portal vein. Several other types of obstructive lesions have been reported. When the disease process occurs in younger persons, especially in early childhood, an omphalitis with an extending thrombosis is to be suspected. Anatomic anomalies, such as stenosis in the portal system or its immediate tributaries, are occasionally observed at the time of operation. An interesting group of such anomalies has been described by Rousselot.² Cavernomatous transformation of the portal vein occurs but is relatively rare. Only one proved case was found in the 70 cases studied in this clinic.

Although some type of obstruction is assumed to be present, it frequently is not possible at the time of operation, even with a routine liver biopsy, to determine the exact site or type of the lesion. Of 55 patients subjected to splenectomy, Rousselot was able to demonstrate a proved obstructive lesion in only 60 per cent.³ Failure to find an obstructive lesion in the extrahepatic venous system does not justify the assumption that no intrahepatic obstruction exists, even though the liver may appear grossly normal.

Most observers concur that the order of sequence is the presence or development of an obstructive lesion, with a gradual increase in portal hypertension sufficient to cause an increasing splenomegaly. At an indeterminate stage in the development of the splenomegaly, evidence of a hypersplenism may be found in the peripheral blood and in the bone marrow. Since the portal system is devoid of valves, collateral circulatory changes develop. The extent of this collateral circulation is obviously predicated upon the type and location of the obstruction and the duration of the disease process. The collateral circulation is most marked when the obstructive lesion is intrahepatic or within the portal vein; it is less marked when the obstruction is in the splenic vein proximal to the spleen.

Certain collateral patterns evolve which at operation are helpful in approximating the site of the obstruction. If the splenic vein alone is involved and there is a moderate splenomegaly, there may be dilatation and tortuosity only of the immediate collaterals, the left gastroepiploic and the short gastric veins. If the obstructive lesion is in the portal vein or within the liver, the mesenteric veins around the ascending and descending colon, and the right and left gastroepiploic veins show evidence of involvement. In a late stage there may be enormous dilatation and tortuosity of all collaterals, including the heavy plexus in the lower esophagus.

Both the gross and the histopathologic changes in the spleen are those of a gradually developing congestion. With this increasing circulatory

stasis, there are widening and distention of the venous sinuses with compression of the pulp spaces. Gradual atrophy of the reticulum occurs with connective or fibrous tissue replacement. There is marked thickening of the fibrillar reticulum of the Malpighian corpuscles. Hemorrhages around the trabecular arteries and perifollicular hemorrhages are usually present.

Despite a well elucidated clinical understanding of Banti's syndrome, the disease process is not generally recognized by pathologists as a pathologic entity.

THE RATIONALE OF SPLENECTOMY

Splenectomy has long been regarded as a logical procedure in Banti's syndrome, especially in larger clinics and in medical centers with special spleen clinics. There is not, however, complete unanimity of opinion that splenectomy is an indicated procedure in this disease. I recently heard three eminent hematologists state that they had never had a splenectomy performed in Banti's syndrome. There are, of course, valid reasons for this difference of opinion. This review will attempt to point out a sufficient number of cogent reasons to indicate the value of splenectomy in the earlier stages of the disease.

It seems in order first to have a proper understanding of the effects of splenectomy upon the individual pathologic factors in the disease process. There are four such pathologically altered factors:

- (1) The pressure dynamics of the portal system;
- (2) Hepatic function;
- (3) The hemorrhagic factors, and
- (4) Hematologic changes, including bone marrow and peripheral blood.

These effects should be interpreted as generalizations. It is not to be inferred that they may be translated into comparable postoperative results in an individual case; however, the effects of splenectomy upon these factors should afford a more comprehensive understanding of both the theoretic and predicted postoperative results.

1. *The Pressure Dynamics of the Portal System.* Increased venous pressure occurs proximal to any obstruction. For example, the pulmonary veins may develop increased tension from a constricting mitral stenosis. There is acceptable evidence that portal hypertension is a constant characteristic of Banti's syndrome. According to Thompson et al.,⁴ the level of portal tension increases to 275 to 470 mm. of water in patients with Banti's syndrome accompanied by Laennec's cirrhosis. Even higher pressure readings were found in cases caused by schistosomiasis.

Unfortunately no postsplenectomy portal pressure readings have been made. Empirically at least, if the obstruction should be limited to the splenic vein itself, splenectomy should decrease and perhaps sufficiently relieve the increased venous pressure to the point that collateral circulation would be unnecessary. If the obstructing lesion is in either the portal vein

or within the liver, splenectomy should also have an ameliorating effect upon the portal hypertension by reducing the pressure significantly. This reduction occurs because an estimated 40 per cent of the blood which goes through the portal vein comes from the splenic artery.

2. Hepatic Pathology. For convenience, cases of Banti's syndrome may be classified as those with and those without cirrhotic changes in the liver. For a number of reasons it is important to determine if the obstruction is intrahepatic or extrahepatic. Various hepatic function tests suffice as a rule to indicate if the liver is involved. Accumulated data, including biopsy studies of the liver obtained at the time of splenectomy, indicate that Banti's syndrome is associated with Laennec's type of cirrhosis in approximately 70 per cent of cases. This type of cirrhosis occurs at varying ages, including childhood, but is more commonly encountered in the third and fourth decades. Other types of cirrhosis are rarely associated with Banti's syndrome. Biliary cirrhosis and cardiac cirrhosis are infrequently accompanied by a splenomegaly.

According to Rousselot,² if the obstruction is extrahepatic and cirrhosis is not found to be present at the time of operation, there is little likelihood that it will develop subsequently. He observed 15 cases which did not develop hepatic changes over a period up to 19 years.

The effect of splenectomy upon both the normal and abnormal liver has been studied. If, for example, the obstructive lesion is in the splenic vein, the liver is unaffected and splenectomy should have no effect upon hepatic function. If the obstruction is in the portal vein, extrahepatically, the absence of normal venous circulation through the liver causes no ischemic changes in the hepatic parenchyma; however, under these circumstances of absent or reduced flow, the liver may be more susceptible to hepatotoxins and may develop granular degeneration.

It is the opinion of several writers that splenectomy has no deleterious effect upon an existing cirrhosis, that is, it does not increase the pathologic changes present. On the other hand, it has been postulated that a reduction in the venous pressure load permits a better response of the liver to supportive therapeutic measures, which may encourage regeneration. Opinions vary about the value of splenectomy if a marked Laennec's cirrhosis is present. Most statistical studies indicate that if the degree of cirrhosis is of a severe grade, with marked collateral circulatory changes and ascites, splenectomy is of little or no value; however, there is an occasional report indicating that ascites has disappeared after splenectomy. Certainly there seems to be no justification for splenectomy as a so-called last resort measure.

3. The Hemorrhagic Factors. Hemorrhage is perhaps the greatest single factor determining life expectancy in patients with Banti's syndrome. It may occur preoperatively as epistaxis or hematemesis; it is a frequent immediate and later postoperative complication. Although hemorrhage occurs most frequently in the presence of cirrhosis, it also occurs as a result of extrahepatic obstructive factors without any demonstrable cirrhosis.

The hemorrhagic tendency is influenced by local and systemic causes. Among the local causes is phlebectasia resulting from portal hypertension, with subsequent thinning and ulceration of mucosa, particularly in the lower esophagus. Among the systemic factors which alter the hemostatic mechanism is a thrombopenia which may affect the clotting time. In the presence of an impaired liver function from cirrhosis, there may also be a hypotherbinemia. An increase in total blood volume may also occur, which can be a factor in increasing the portal tension. Both of these conditions contribute to the hemorrhagic tendency.

The incidence of hemorrhage is, as a rule, decreased after splenectomy. Quoted estimates vary, the decrease being estimated at from 33 per cent to 50 per cent. The operation, however, does not necessarily correct the future hemorrhagic tendency, particularly if the obstructive factor is within the liver or within the portal vein. Theoretically, the reduction in the likelihood of hemorrhage should parallel the estimated 40 per cent reduction in the amount of blood supplied to the portal bed by the splenic artery, plus the effect of correcting the preoperative thrombocytopenia.

If hematemesis occurs in Banti's syndrome during the first or second week postoperatively, it is an unfavorable prognostic sign. It usually indicates an extension of the thrombotic process in branches of the portal vein previously nonobstructed.

4. *Hematologic Changes, Including Bone Marrow and Peripheral Blood.* In the early stage of Banti's syndrome the hematologic findings are not always pathognomonic. A similar degree of anemia and leukopenia occurs in many splenomegalic conditions. It is believed that the hematologic changes are related entirely to the influence of the spleen upon the bone marrow. Apparently the site of the obstructive lesion has no influence on the hematologic picture. The characteristic changes of the blood are similar whether there is a splenic vein thrombosis or a moderate degree of cirrhosis. In a late stage of atrophic cirrhosis the erythroid cells may develop a macrocytic character.

In Banti's syndrome, as in various types of pathologic splenomegalies, there may be a hypersplenic effect with an inhibition of the maturation process in the bone marrow, affecting particularly the erythroid elements. These changes have been well summarized by Limarzi, Jones, Paul and Poncher.⁵ These writers enumerate the progressive changes which occur in three phases of the disease. In the earliest stage the marrow shows a myeloid hyperplasia, and there is a moderate anemia and leukopenia peripherally. As the splenomegaly increases, the marrow shows a "maturation arrest" of the myeloid and megakaryocytic tissue with a peripheral leukopenia, neutropenia, thrombocytopenia and myeloid immaturity. Later, with an advanced degree of cirrhosis of the liver, the marrow shows a marked erythroid immaturity in addition to the changes in the myeloid tissue described above. These progressive changes indicate that a study of the bone marrow may be of considerable prognostic significance, and a definite aid

in evaluating the advisability of operation as well as the results to be expected from splenectomy.

The characteristic thrombocytopenia has much clinical significance. It is thought to occur from a reduction in the number of platelets produced by the megakaryocytes, although some writers have expressed the belief that it is a result of increased destruction of the platelets in the enlarged, over-distended spleen. The thrombocytopenia is immediately corrected by splenectomy; in fact, there is quite often an overcompensation in the production of thrombocytes during the first few weeks postoperatively. Greatly increased counts of 1,000,000 to 2,000,000 platelets may continue for a number of weeks. This thrombocytosis, of course, greatly increases the postoperative thrombotic hazard. For this reason, patients with a preoperative thrombocytosis are poor operative risks.

Splenectomy relieves the hypersplenic effect upon the peripheral blood, although the bone marrow may remain hyperplastic. With occasional exceptions, the secondary anemia, leukopenia and thrombopenia are restored to normal. The functional restoration of the bone marrow is one of the most favorable results of splenectomy in Banti's syndrome.

A Recapitulation of the Effects of Splenectomy. The postoperative effects upon four pathologically altered factors in Banti's syndrome may thus be summarized:

Increased venous pressure associated with an obstructive lesion in the splenic vein should be entirely relieved by splenectomy. Increased portal pressure should be decreased by an estimated 40 per cent.

Splenectomy is rarely followed by a developing cirrhosis if hepatic changes do not previously exist; splenectomy does not accelerate an existing cirrhosis; a reduction in the portal load may offer a better opportunity for hepatic regeneration.

Splenectomy corrects the thrombocytopenia which, with other factors, reduces the likelihood of future chronic hemorrhage by an estimated 33 to 50 per cent.

The operation favorably influences the preoperative maturation arrest of the bone marrow with a normal restoration of the peripheral blood elements.

This review of the effects of splenectomy upon the individual factors which are deranged in Banti's syndrome indicates that there is a sound basis for the operative procedure. The time factor is obviously an important one. For the best results, decision about the advisability of splenectomy should be reached without undue delay. Except in those few cases in which the splenic vein alone is involved, the operation by no means entirely corrects the disease process. For the most part it modifies the course of the disease by improving bone marrow function and decreasing hemorrhage. This attempt to improve the patient's status by splenectomy is mitigated by other hazards incident to the operation. A brief review of our own statis-

tical data, as well as current figures in the literature, will indicate the degree of these hazards.

STATISTICAL REVIEW

The writer has reviewed the case records of 70 patients seen in the Henry Ford Hospital and diagnosed as *splenic anemia*, *Banti's syndrome* and *congestive splenomegaly*. Thirty-one of these 70 patients were subjected to splenectomy. Three patients died within 24 hours from hemorrhage at the site of operation. Three other patients died from thrombosis and embolism before the fourteenth day; hence, the immediate operative and postoperative mortality was 19.3 per cent. Fifteen more of the 31 patients are known to be dead; nine had subsequently died of hemorrhage, and six had died of other causes. Five other patients were known to be alive 10, five, three, two and one and a half years postoperatively. Two additional survivors indicate in a conspicuous way the value of splenectomy in an early phase of the disease. One patient had a splenectomy 22 years ago, the other 23 years ago. Neither patient had any postoperative hemorrhage and both are perfectly well today.

In considering these mortality figures, it is only fair to point out that several of these patients had an advanced degree of cirrhosis with ascites, and in the light of current knowledge a splenectomy would not be considered an advisable procedure. The figures have been quoted for two reasons: first, because they probably represent a cross section of average results in many hospitals; and second, because they are fairly typical of much of the published data concerning postoperative results.

The method used by most writers to evaluate the results of splenectomy is to quote the postoperative span of life and the mortality rate. These tables of figures show a decided variation, as might be expected. It is difficult to group for comparison cases with similar characteristics. Even cases with proved cirrhosis may have other influencing factors—such as duration, degree of involvement and age of the patient—which make comparisons difficult. Furthermore, the two criteria are seldom presented with comparative control data concerning nonsurgically treated cases. Most published results concerning splenectomy in Banti's syndrome would have the reader infer that the operation offers clear-cut and decisive advantages. The over-all average of results does not suggest that this impression is a correct one. Only one report, which affords a contrast of results in similar types of cases with and without operation is available for consideration. Howells⁶ in Wales published in 1938 his studies of 94 patients, 43 of whom were treated medically and 51 of whom had a splenectomy. He concludes that splenectomy does not increase expectation of life, does not modify the progress of cirrhosis, and does not decrease the occurrence of postoperative hematemesis. He does not believe that splenectomy should be carried out as a routine procedure.

No attempt will be made to quote accumulated statistics. The results of

Pemberton's⁷ statistics on splenectomized cases show the lowest mortality rate and the longest postoperative span of life. In his series of 215 cases, only 9.8 per cent died in the hospital; 54.6 per cent of the remaining patients lived five years, 41.5 per cent of the group lived 10 years, and 20.4 per cent lived 20 years or longer. More typically average results are evident in the report of Eliason and Johnson⁸ in 28 cases of splenectomy. Their mortality rate was 25 per cent, seven of the eight fatal cases having extensive damage to the liver. Twenty-eight per cent lived five years and 25 per cent lived 10 years. As a rule, the results of splenectomy in children are better than in adults. Of eight cases reported by Diamond,⁹ there were only two postoperative deaths; the six other patients were well six to 10 years later.

Most reports indicate that the average operative mortality is usually high even in well known clinics. From seven published sources, which include a review of the results of 543 cases of splenectomy, the respective mortality percentages are 9.6, 12.4, 14.5, 25, 25 and 40. The average, therefore, is 21.6 per cent. Several factors contribute to this high mortality rate. Almost every reported series includes a number of cases with advanced cirrhosis and ascites. The results of splenectomy in this group are almost universally poor. Most reports include all cases of splenectomy in the hospital records; some of the operations were performed two, three or more decades ago. The application of newer technics in the selection of cases should offer more promising results. Interpretation of the preoperative platelet count, hepatic function studies, liver biopsy at the time of operation for better etiologic classification, and an intensive preoperative therapeutic period designed to improve the function of the remaining hepatic tissue should assist in reducing the current postoperative mortality rate.

It is therefore apparent that, on the basis of published statistics, the results of splenectomy in Banti's syndrome are on the whole far from ideal. If better results are to be obtained, there must be a careful discrimination in the selection of cases for operation. A number of criteria must be considered as they apply to the individual patient.

CONTRAINDICATIONS FOR SPLENECTOMY

There are a number of distinct contraindications for the operation. If the following factors are given adequate consideration preoperatively, the current high operative mortality rate in Banti's syndrome can be lowered significantly:

Splenectomy is rarely justified in progressive decompensating liver disease.

The operation is not justified in the presence of a preoperative thrombocytosis, because of the increased danger of postoperative thrombosis and embolism. Even a normal preoperative platelet count is frequently followed by an excessive thrombocytosis postoperatively.

The results of splenectomy are invariably poor if the bone marrow shows evidence of a toxic depression rather than the characteristic hyperplasia.

A further contraindication is an erythroblastic bone marrow with a reversal of the myeloid-erythroid ratio.

It has also been emphasized that the operation is contraindicated in children whose blood picture is not entirely typical.

A severe degree of anemia may also be an immediate contraindication for the operation.

SUMMARY

From a review of all published data on this subject, the following statements seem acceptable for clinical guidance:

Splenectomy reduces portal hypertension and thereby reduces the hemorrhagic tendency in this disease.

The hemorrhagic tendency is further reduced after correction of the preoperative thrombocytopenia by splenectomy.

The operation has no unfavorable effect upon hepatic function, and may afford some improvement in function by reducing the portal load.

Splenectomy corrects the hypersplenic effect upon the bone marrow, and restores normal function with correction of the peripheral pancytopenia.

The results of splenectomy in children are usually more satisfactory than in adults. If the disease is not discovered until after the age of 40, the operative mortality results are decidedly higher than in earlier years.

Splenectomy cures the small group of cases in which the obstruction is limited to the splenic vein.

The operation is also beneficial to those patients with a moderate degree of cirrhosis who have not had preoperative hematemesis, and in whom extensive collateral circulatory changes have not developed.

If patients have had hematemesis preoperatively, approximately 50 per cent will continue to have hemorrhage postoperatively.

The hemorrhagic tendency is not aggravated by splenectomy.

Almost uniformly poor results occur postoperatively in patients who have advanced cirrhosis and ascites.

All evidence indicates that the best postoperative results are obtained in those cases in which splenectomy is carried out in an early stage of the disease.

CONCLUSIONS

There is a sound basis for splenectomy in properly selected cases of Banti's syndrome.

The benefits to be derived from splenectomy are inversely proportional to the progress of the disease.

Some few patients are completely restored to health and live a normal span of life.

In a majority of cases the operation serves as a palliative measure which modifies the course of the disease.

The high operative mortality has as its basis a number of factors which to a large degree can be evaluated before operation.

Several conditions may exist, any of which may be a contraindication to splenectomy.

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INSULIN AND THE CAROTID SINUS*

By ISADORE RUDNIKOFF, B.S., M.D., F.A.C.P., *Yonkers, New York*

THE importance of the carotid sinus reflexes in relation to cardiovascular physiology is well known. In 1886 Czermack^{1, 2} showed that pressure on the neck in the region of the vagus nerve caused slowing of the heart. The basic work of Hering³ from 1923 to 1932 laid the foundation for future investigations. His studies, with those of de Castro⁴ in 1927, were responsible for our present knowledge of the anatomy and histology of the carotid sinuses. Between 1929 and 1937 a long series of researches^{5, 6, 7, 8, 9, 10, 11, 12, 13} was reported with respect to the physiologic and pharmacologic behavior and relationships of the sinuses. During this period the various clinical patterns of the carotid sinus syndrome were described.^{14, 15, 16}

The increased sensitivity of the carotid sinuses to stimulation in patients with arteriosclerosis, hypertension and coronary artery disease has been stressed by Mandelstamm and Lifschitz,¹⁷ Weiss and Barker¹⁴ and Sigler.^{18, 19, 20, 21} No relationship between individuals with diabetes mellitus receiving insulin and the carotid sinus syndrome was mentioned. Indeed, Sigler^{18, 22} in his extensive clinical reports on 1,193 cases simply mentions diabetes as one of the various disease states in which the syndrome might be observed.

The effects of insulin upon the sympathetic and parasympathetic nerves have been reported in several investigations. However, the effects, if any, of this hormone upon the carotid sinus reflexes have not been clearly set forth. Our attention was brought to this subject by a series of unusual circumstances which occurred in a case of diabetes mellitus. During the treatment the question arose whether insulin could increase or exaggerate the effects noted during carotid sinus stimulation. A summary of the patient's clinical course will readily demonstrate the problems which arose. They were of sufficient importance to form the basis of the investigations herein presented.

CASE REPORT

A 63 year old woman was seen on August 8, 1943. Her complaints consisted of pruritus, arthralgias, dyspnea upon exertion, polyuria and polydipsia. Her past history was not significant. Examination showed a markedly obese female, 54 inches tall and weighing 210 pounds. Her blood pressure was 180 mm. Hg systolic and 100 mm. diastolic; the pulse was 80. Both eyes showed moderate diabetic retinitis. The heart sounds were very distant. There was no evidence of congestive failure. Three large aprons of fat were present over the abdomen. The fasting blood sugar was 350 mg. per hundred c.c., and the urinary sugar 4 plus. She was given a 1,400 calorie diet and advised to take 30 units of protamine zinc insulin each morning. The patient was observed at regular intervals for one year, during which time her blood sugar dropped to 110. Her weight, blood pressure and pulse rate were constant.

* Received for publication September 15, 1949.

The patient was not seen again until June 8, 1948. She complained of polyuria, nocturia, polydipsia and generalized pruritus. She had been taking 15 units of protamine zinc insulin but admitted being careless with her food. She stated that she had had "fainting spells" on several occasions. Her weight was 223 pounds, the blood pressure 180 mm. Hg systolic and 90 mm. diastolic, and the pulse 76. There were large abrasions and contusions on her forehead. Signs of early congestive failure were present. The fasting blood sugar was 312 mg. Pressure on the right carotid sinus in the fasting state showed a drop in heart rate of about 18 beats, but no effects were noted on the left. The blood pressure was not significantly affected, and the patient did not experience any untoward symptoms. She was placed on a 1,200 calorie diet, with 35 units of protamine zinc insulin.

The patient was next seen three weeks later. She stated that she had had several attacks of "insulin shock" at varying times during the day and had become dizzy and faint. The blood pressure was 170 mm. Hg systolic and 100 mm. diastolic, and blood sugar 219 mg. Pressure over both carotid sinuses one and one-half and three hours after insulin administration produced alarming cardiac standstill for at least seven seconds. Because of this clinical picture, the patient was given 1 c.c. of tincture of belladonna, 15 mg. of phenobarbital and 30 mg. of ephedrine sulfate four times daily. She experienced no further episodes of dizziness or syncope, but when she attempted to discontinue her medications she suffered a return of her previous symptoms. Her carotid sinuses were stimulated on two other occasions, before and after insulin, and the results previously described were again noted.

On September 21, 1948, the patient was found in a state of collapse. Her pulse rate was six per minute and the blood pressure 100 mm. Hg systolic and 60 mm. diastolic. She had discontinued her tincture of belladonna and ephedrine sulfate because of blurring of vision and palpitation, but had continued to take her insulin. She responded rapidly to atropine and epinephrine subcutaneously and was then hospitalized for further study. A dilemma was reached when the patient developed syncope with bradycardia with each dose of unmodified insulin. She recovered with epinephrine and atropine, but as this process was repeated the blood sugar continued to rise until a level of 480 mg. was reached and signs of ketosis appeared. In order

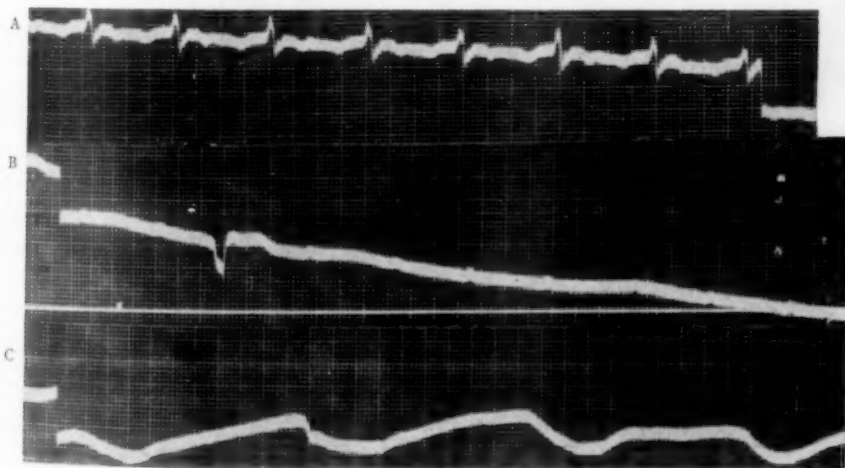


FIG. 1. Portions of electrocardiograms belonging to case 10. A represents Lead II one month before death. B and C show ventricular standstill in Lead II and CF₆, respectively, after insulin and carotid sinus stimulation.

to overcome the latter, parenteral fluids and electrolytes were given with insulin. Despite all treatment, the patient died following cardiac asystole. Portions of her electrocardiogram are shown in figure 1. Other details in relation to pulse rate changes are included in table 1.

It appeared from this that insulin, whether protamine zinc or unmodified, increased the sensitivity of the carotid sinus reflex to such an extent as to produce drastic symptoms. Our problem, then, was whether similar effects could be reproduced in other patients with diabetes.

METHOD

Ten patients with diabetes mellitus were studied, including the one already described. All had been under observation for their diabetes for periods of months to years and had been investigated from all points of view. All except cases 3, 4 and 5 were receiving insulin as part of their daily routine. Patient four had taken insulin but it was discontinued for reasons which will be discussed later. Cases 2 and 6 were maintained on daily doses of 50 mg. of propylthiouracil. Case 7 required 15 units of concentrated liver extract every 10 days, and case 8 took 0.2 mg. of digitoxin each day.

Each individual appeared in the office in the early morning. A fasting blood sugar and electrocardiogram were taken with the patient in a semi-sitting position on the examining table. The right and left carotid sinuses were each stimulated for 15 to 25 seconds by means of simple finger pressure and massage, and Lead II was taken during this procedure. The patients were then given unmodified insulin, the doses depending upon the fasting blood sugar level. At one, two and three hours after insulin, venous blood was drawn and analyzed for glucose. Lead II was then recorded before and during right and left carotid sinus pressure. The patients' symptoms were noted during all phases of the study.

In cases 1, 6 and 7, the fasting blood sugars were lower than anticipated, since all three had moderately severe diabetes. These patients admitted increasing their doses of insulin beyond the amounts suggested to them previously. To eliminate the occasional cardioinhibitory effects seen in insulin hypoglycemia, all patients having a blood sugar under 80 mg. were given appropriate amounts of either orange juice or dextrose. A period of a half-hour was then allowed before the carotid sinuses were stimulated.

OBSERVATIONS

To simplify the tabulations of our results and their evaluation, three factors were studied: Changes in the heart rate and blood pressure, the presence or absence of dizziness and related symptoms, and the production of syncope. In measuring the heart rate on the electrocardiograms, a period of 10 seconds, beginning with the first sign of cardiac slowing, was uni-

formly used. The blood pressure readings were determined by standard manometric methods.

The decreases in heart rate with carotid sinus pressure and related data are summarized in table 1. "R" and "L" indicate the drop in rate with

TABLE I
Decrease in Heart Rate with Carotid Sinus Pressure

Case No.	Age	Sex	Diagnoses	Fasting Blood Sugar	Before Insulin	Units Insulin	1 Hour After Insulin		2 to 3 Hours After Insulin	
							Blood Sugar	Change in Pulse Rate	Blood Sugar	Change in Pulse Rate
1	21	F	Diabetes	98	R 0 L 12	15	74*	R 6 L 6	107	R 24 L 18
2	41	F	Diabetes Hyperthyroidism	228	R 12 L 0	20	208	R 18 L 12	134	R 30 L 18
3	43	M	Diabetes Hypertension Osteoarthritis	139	R 0 L 0	15	114	†R 0 L 0	85	†R 6 L 6
4	44	M	Diabetes Obesity Carotid sinus syndrome	123	R 12 L 18	20	111	R 16 L 10	89	R 24 L 6
5	45	M	Diabetes Hypertension	163	R 16 L 16	15	90	R 22 L 16	90	R 24 L 12
6	52	F	Diabetes Hyperthyroidism	107	R 6 L 6	15	86*	R 28 L 16	110	R 20 L 32
7	54	M	Diabetes Pernicious anemia	80*	R 22 L 28	12	136	R 48 L 24	60* plus	R 36 L 30
8	55	M	Diabetes Chronic bronchitis	250	R 18 L 42	28	227	R 42 L 48	132	R 36 L 44
9	61	F	Diabetes Pleural calcification	211	R 30 L 0	32	118	R 36 L 0	63* plus	R 24 L 24
10	63	F	Diabetes Obesity Carotid sinus syndrome	234	R 18 L 0	35	196	R 72 L 66	170	R 72 L 60

* Patient given glucose before carotid sinus stimulation.

† This case showed a drop in B. P. from 160/110 to 86/60 at one hour, and from 160/110 to 60/30 at 2 to 3 hours.

pressure on the right and left carotid sinuses. It will be noted that, while cardioinhibitory effects of varying degrees were obtained in nine of the 10 patients before insulin was given, more decisive and greater reductions in heart rate were recorded one, two and three hours after the administration of the insulin. The Fisher test was applied and indicated a P of 0.01 and

less than 0.001 for the changes in heart rate one hour after insulin and two to three hours after insulin, respectively. Thus the changes after insulin are highly significant. Case 3 showed no response of any type until one and three hours after insulin, but here the effects were predominantly vaso-depressor. In analyzing these results, it can be seen (1) that no relationship existed between the blood sugar levels and the extent of carotid sinus response, and (2) that a patient showing sensitivity of one carotid sinus reflex can, after insulin, develop increased sensitivity of the other or both.

Mandelstamm and Lifschitz¹⁷ noted that the patients in the older age groups, especially those with hypertension and arteriosclerosis, showed more striking responses to carotid sinus stimulation. This was emphasized by Weiss, Barker, Ferris and their co-workers.^{14, 15, 16} In the large group of cases observed by Sigler,^{18, 23} individuals with coronary artery and other types of heart diseases were included in this category. In our own series, small as it is, we were able to produce marked effects after insulin in one patient aged 21 years and in four between the ages of 40 and 45 as readily as in those of the sixth and seventh decades. There was no appreciable difference in the behavior of either sex.

TABLE II
Summary of Effects Produced by Carotid Sinus Pressure

	Dizziness	Syncope
Before insulin	40%	10%
One hour after insulin	90	50
Two to three hours after insulin	100	80

Sigler²² noted that approximately 40 per cent of patients reacting to carotid sinus pressure complained of dizziness and related symptoms. In our study, four of 10 patients showed these effects before insulin. However, at one and two to three hours after the injection of insulin, this group of symptoms was elicited in 90 and 100 per cent, respectively (table 2). Here, again, there was no relationship to hypoglycemia. The data presented in this table were subjected to the Chi-square test, and the results were statistically significant in every case.

Syncope as a symptom of carotid sinus reflex hyperactivity may occur as a result of three different mechanisms. Weiss and Barker¹⁴ classified these as the vagal, vasodepressor and cerebral types. Generally speaking, this occurred in approximately 14 per cent of the cases studied.²² In the series presented here, one case developed syncope with muscular twitchings before insulin. One and two to three hours after insulin, unconsciousness occurred in 50 and 80 per cent, respectively (table 2). Of these, one was a purely vasodepressor response, while the others were all associated with striking reductions in heart rate. It is interesting to note in this respect that three of the patients in the older age groups developed contralateral numbness and paresthesias which persisted for several minutes after con-

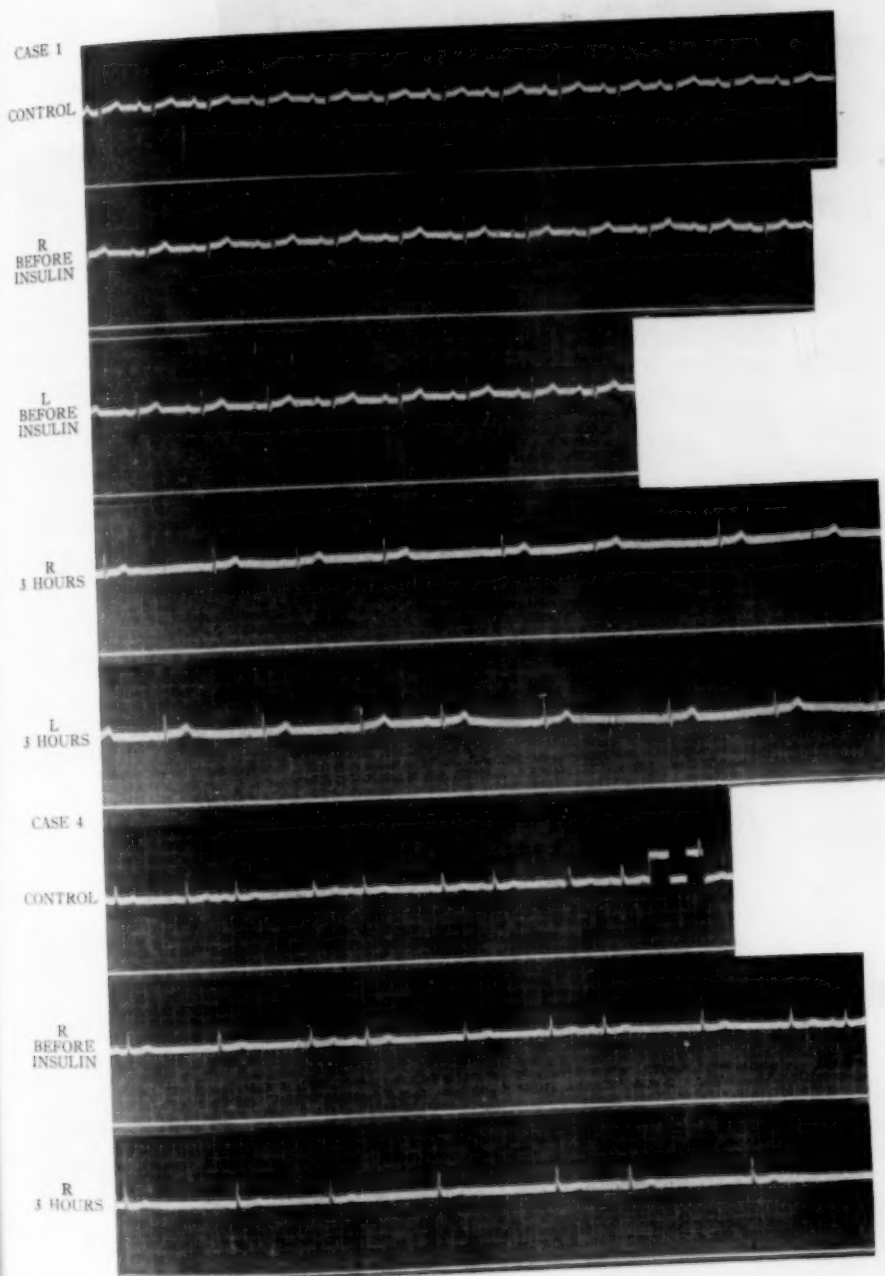


FIG. 2.

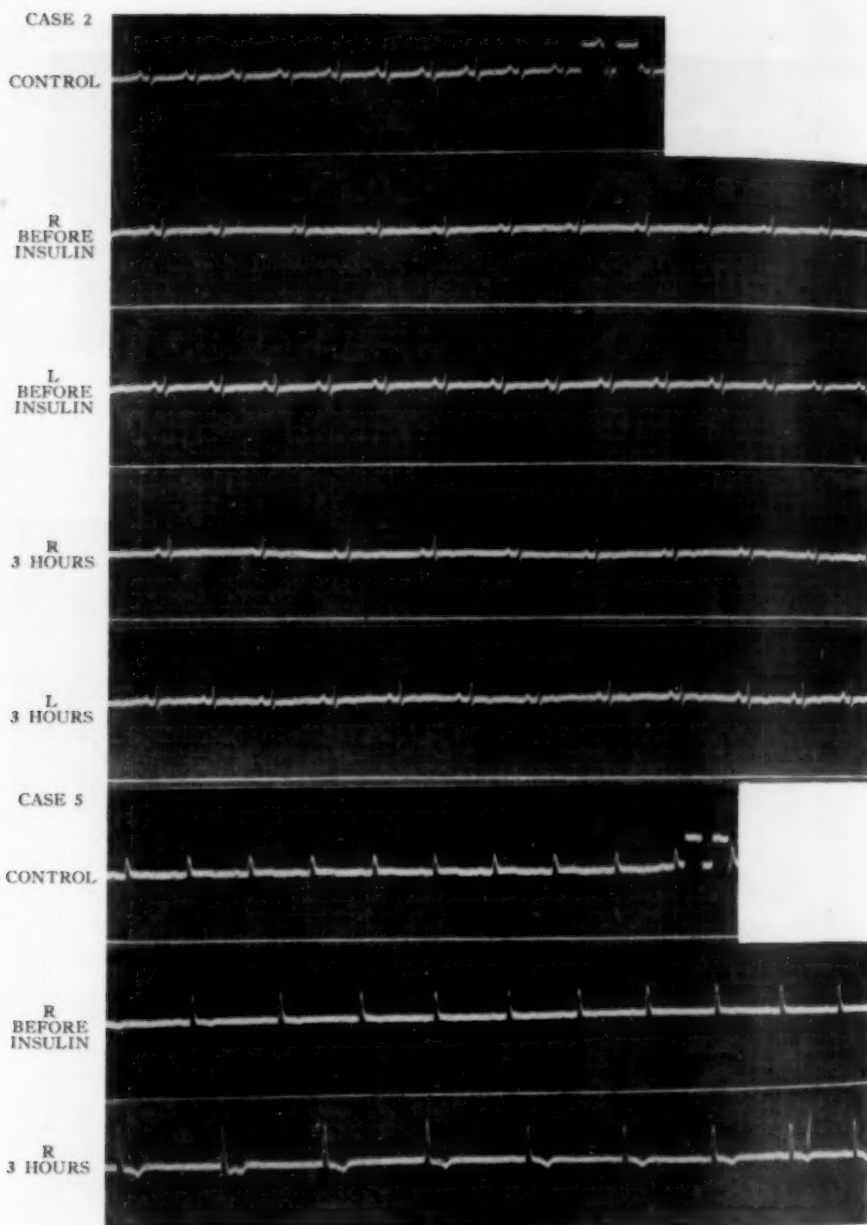


FIG. 3.

sciousness returned. These occurrences emphasize the profound cerebral changes which might occur, especially in patients with marked hypertension and advanced arteriosclerosis. Indeed, Marmor and Sapirstein,²⁴ Askey²⁵ and Zeman and Siegal²⁶ have stressed the dangers of carotid sinus stimula-

tion in elderly patients because of the possibility of inducing serious and permanent lesions of the central nervous system.

In respect to syncope, special mention should be made of case 4. This man was seen because of repeated episodes of unconsciousness. These could be reproduced readily by carotid sinus stimulation while he was receiving insulin as part of the treatment for his diabetes. When the insulin was discontinued he ceased to have syncope. The latter quickly recurred when daily injections of the hormone were again given.

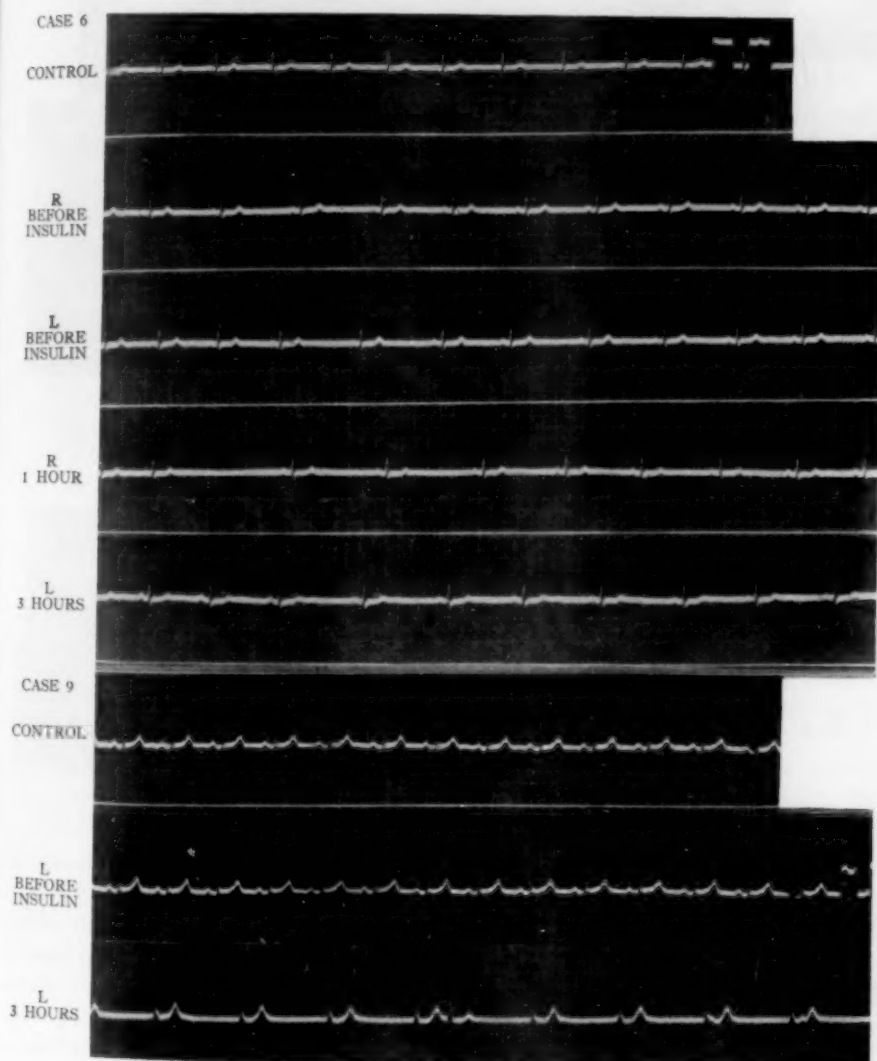


FIG. 4.

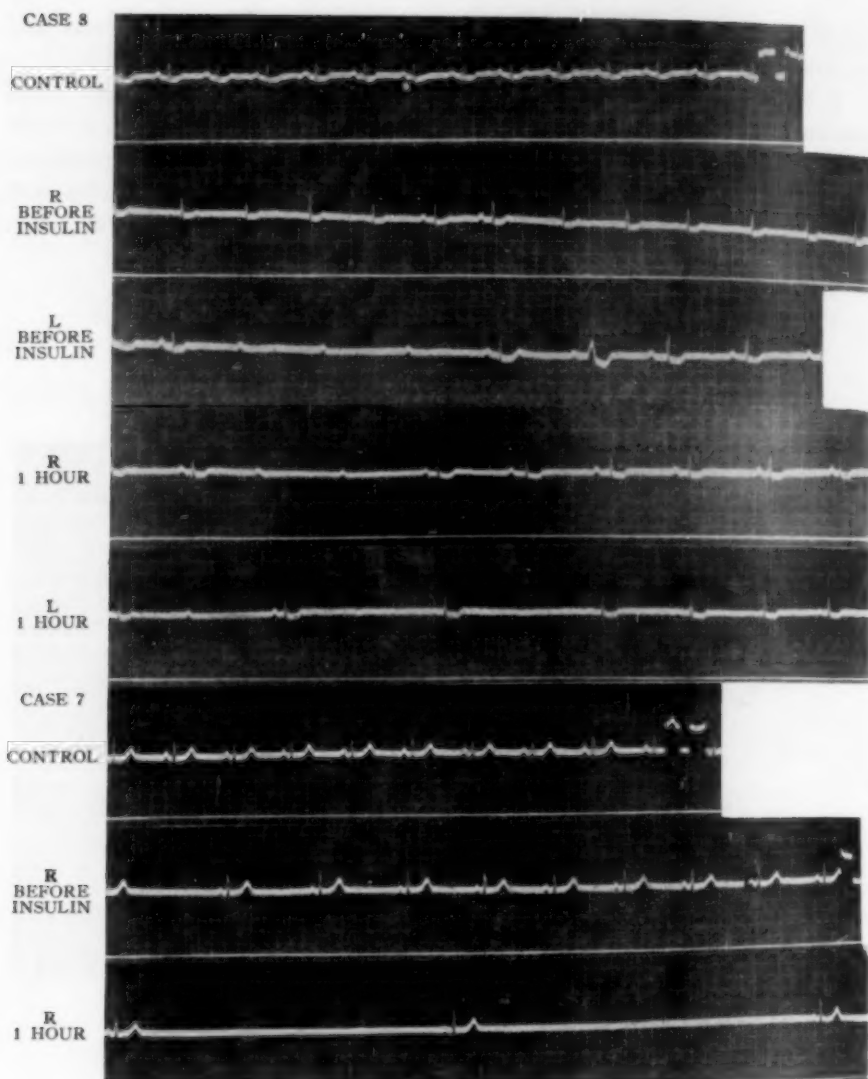


FIG. 5.

The varied electrocardiographic changes which can be induced by carotid sinus stimulation have been fully described by Weiss and Barker,¹⁴ Sigler,²⁷ Koffler and Alexander,²⁸ and Engel, Romano and McLin.²⁹ These included varying degrees of A-V block, bizarre QRS complexes, bundle branch block, prolongation of the P-R interval, RS-T wave depressions and cardiac standstill. Several of these changes were observed in our own group. However, since this study involved primarily the changes in heart rate before and after insulin, Lead II was used exclusively for comparative measure-

ments. Figures 2 through 5 demonstrate the effects of carotid sinus pressure under such circumstances. They show in a graphic manner differences which occurred. "Control" indicates Lead II before insulin, while "R" and "L" signify this lead during right and left carotid sinus stimulation at the time intervals mentioned.

DISCUSSION

The effects of insulin upon the autonomic nervous system have been documented in many reports since the discovery of this hormone. In 1924, Cannon, McIver and Bliss³⁰ demonstrated that hypoglycemia-inducing doses of insulin could stimulate the sympathetic division. Very shortly thereafter, evidence was advanced to prove that insulin was readily able to incite the parasympathetic nerves to increased activity.

Bulatao and Carlson³¹ in 1924 showed that insulin was able to increase the rate and intensity of hunger contractions, while Quigley and Templeton,³² in 1930, stated that this would not occur if the vagi were sectioned. The secretory effects induced by such procedures were studied by Babkin³³ and many others. This work formed the basis of the presently used insulin test described by Hollander³⁴ and Winkelstein³⁵ for the presence of intact vagus fibers after "complete" vagotomy.

Other effects of insulin upon the parasympathetic nervous system include an increase in salivary flow³⁶ and constriction of the pupil, both overcome by the injection of atropine.^{37, 38} Although tachycardia is the more common finding in insulin shock, decrease in the heart rate has been reported frequently. This was demonstrated by Garrelon and Santenoise,³⁹ von Haynal and his co-workers,^{40, 41} Schäffer and his group,⁴² and Wettgenstein and Mendel,⁴³ and was attributed to vagotonic action. In 1931 Dworkin⁴⁴ reported the effects of insulin in normal cats and those which had undergone sympathectomy and vagotomy. He concluded that cardiac acceleration was due to central sympathicoadrenal impulses and that slowing resulted from both central vagus stimulation and peripheral action. He added that during insulin hypoglycemia, while both divisions of the autonomic nervous system were stimulated, the vagus effects predominated in organs that were innervated by both sets of nerves.

The anatomic relationships of the carotid sinuses to the vagus nerves have been well established since the work of Hering³ and de Castro.⁴ In the fields of physiology and pharmacology, extensive work has been done by Heymans and his co-workers,^{5, 6} Nathanson,⁹ Schmidt,^{7, 8} and von Euler and Liljestrand.^{11, 12, 13} These workers described the physicochemical effects of various drugs and substances upon the carotid sinus reflexes. Of these, it was Heymans⁵ who suggested that the sinuses may have a regulatory effect upon blood sugar levels and that the action of insulin may in some way be controlled in these areas. He was thus the first who suggested some relationship between insulin and the carotid sinuses. Casas and Hinsberg⁴⁵ did confirmatory work along these lines. However, Thelen,⁴⁶ in extensive ex-

periments using rabbits, concluded that there was no experimental proof that the carotid sinuses can regulate the blood sugar content. In 1929 R  ih  ,⁴⁷ and in 1931 R  ih   and Malm⁴⁸ reported that insulin decreased the sensitivity of the cardiac vagus in the rabbit. They ascribed this effect to the increased potassium ion content of the heart muscle. Harrison and Finks⁴⁹ expressed the belief that a relationship existed between hypoglycemia and increased carotid sinus reflex activity. They observed spontaneous attacks of syncope due to carotid sinus pressure three or four hours after meals.

Our own studies herein reported demonstrated repeatedly that insulin can increase the effects resulting from carotid sinus stimulation. The hormone may affect the vagus center so that ordinary impulses from any part of the body to it can produce exaggerated responses. The carotid sinus receptors thus serve as a convenient way of influencing vagus mechanisms. The hypoglycemic effect of insulin was eliminated by using comparatively small doses of the hormone and by the administration of glucose whenever blood sugar levels fell below 80 mg. In three of the cases, where both syncopal and cardioinhibitory effects were observed, atropine and its derivatives were used with insulin as part of treatment and were effective in eliminating these symptoms. Withdrawal of the insulin in two patients yielded the same beneficial results. These experiments were repeated on several occasions and showed essentially the same responses.

This study was performed upon patients with diabetes rather than normal ones because of the greater sensitivity of the former to insulin. It might be expected that normal subjects would react similarly if sufficiently large doses of the insulin were employed. Such a study has been begun. While the data collected are not sufficiently numerous to be statistically significant, comparable findings, especially in the older age groups, have been obtained. Eventually they will be made part of a separate report.

The effect of ordinary carotid sinus impulses may be greatly exaggerated in some conditions. One of these is following insulin. Clinicians treating patients with diabetes have seen some who have had reactions which simulated and were attributed to insulin shock. It has been our experience that if blood sugar levels were to be determined during these episodes, normal or elevated amounts would not infrequently be found. It is our contention that some of these occurrences are actually vagal effects similar to those seen in carotid sinus syndromes. The clinical importance of such findings is self-evident.

Individuals with diabetes who receive insulin must occasionally submit to surgery. These patients are subjected to the action of the insulin, to the increased CO₂ concentration from anesthesia, and to the effects of traction and pressure on the neck. These three factors tend to stimulate or increase the sensitivity of the carotid sinuses. They can well serve as a plausible explanation for some of the so-called anesthetic deaths in which cardiac asystole occurs. It would perhaps be judicious to record the reactivity and

sensitivity of the carotid sinuses in all such patients undergoing surgical procedures with general anesthesia.

CONCLUSIONS

1. Data are presented showing the effects of insulin upon the carotid sinus reflex in a group of 10 patients with diabetes mellitus.
2. Results of these studies suggest that in such patients (a) insulin increases the activity of the carotid sinus reflex, and (b) insulin is capable of stimulating the cardiac vagus at nonhypoglycemic levels.
3. The clinical implications of these findings are mentioned.

The author is indebted to Mrs. Ruth B. Higgs for her valuable technical assistance.

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AN EVALUATION OF RIGID DIETARY SODIUM RESTRICTION IN THE MANAGEMENT OF ASCITES IN CIRRHOSIS OF THE LIVER *

By CHARLES R. LOWE, M.D., *Casper, Wyoming*, and DONALD C. OVERY, M.D., *Ann Arbor, Michigan*

THIS study was undertaken in an effort to evaluate the possibility of diminishing and preventing the formation of ascites in patients with hepatic cirrhosis by restriction of sodium intake in conjunction with the use of diuretics. If such patients could be spared the discomfort of massive ascites and frequent abdominal paracenteses without causing an unfavorable effect upon their disease in general, the procedure would be considered worthwhile.

In the first decade of the present century, articles appeared in the French literature ^{1, 2, 3} advocating the restriction of sodium chloride in the diet as a means of retarding the formation of ascites in hepatic cirrhosis. The dietary restriction of salt in the management of this disorder was widely accepted for a number of years. Subsequently, the enthusiasm for high protein, high carbohydrate and liberal vitamin intake in the treatment of chronic liver disease led to disregard of the sodium content of the diet. Until protein supplements low in sodium content became available, it was difficult to limit the sodium intake on the latter regimen to the point that accumulation of extracellular fluid could be prevented.

RELATION OF SODIUM RETENTION TO FORMATION OF ASCITES

The organism has the capacity normally to maintain a nearly fixed concentration of each of the electrolytes in the extracellular fluid. Ascites is merely an increase in the volume of extracellular fluid. The retention of fluid requires a proportional retention of sodium to the extent of 140 mEq. per liter of water. Granting that these patients still possess the capacity to maintain a normal concentration of sodium in the extracellular fluid, they will be unable to increase the volume of extracellular fluid (accumulation of ascites) when the intake of sodium is so low that no significant amount of it can be added to the organism. Since the minimal sodium loss from the skin and feces is approximately 150 mg. (6.5 mEq.) per 24 hours, a diet containing 200 mg. (8.7 mEq.) of sodium per day will require the organism to reduce the renal loss of sodium to 50 mg. (2.2 mEq.) or less per 24 hours to maintain sodium balance. Even if the urine became sodium free, the individual would retain only 50 mg. (2.2 mEq.) of sodium daily on this diet. Accordingly, 64 days would be required to accumulate 1 L. of fluid

* Received for publication January 13, 1950.
From the Department of Internal Medicine, University of Michigan.

containing 140 mEq. of sodium. Only when the organism has lost its capacity to maintain a normal concentration of sodium can extracellular fluid accumulate more rapidly by permitting dilution of the electrolytes.

METHODS

Patients with cirrhosis with ascites were accepted for study as they arrived on the medical wards, without attempt to select only those who would adhere to the dietary regimen. The diagnosis of portal cirrhosis was based upon the clinical history, typical physical findings, roentgen-ray studies and a "battery" of liver function studies. Liver function tests employed were: total blood bilirubin determination, with separation of the free and combined fractions¹¹; total serum protein determination, with separation of the albumin and globulin fractions¹²; bromsulfalein retention¹³; cholesterol and cholesterol esters determination¹⁴; urine urobilinogen determination¹⁵; thymol turbidity¹⁶ and gamma globulin¹⁷ values; cephalin cholesterol flocculation,¹⁸ and prothrombin concentration.¹⁹

All patients were placed at modified bed-rest, with bathroom privileges as tolerated. The oral intake of fluids was encouraged, with no attempt at restriction of total amount. In no instance was it necessary to administer supplementary parenteral fluids. The diet contained approximately 200 mg. of sodium and 58 gm. of protein daily. In order to comply with the current view, which advocates the use of diets high in protein in the treatment of chronic liver disease, the protein content of our diet was increased with supplementary Casec or Lonalac.* In most instances, 100 gm. of Casec was given in the form of four glasses of chocolate-flavored substitute containing 88 gm. of protein and providing a total protein intake of 146 gm. daily. The Casec added only 40 mg. of sodium per day or, if the low sodium product was used, only 13 mg. of sodium per day. A similar program was used with Lonalac but, since this product contains only 27 per cent protein, larger amounts of it were required to produce a high protein diet. The sodium content of Lonalac is negligible (0.02 per cent). The supplementary products were given with the meals throughout the day and, when properly flavored, were well tolerated by the patients. Unless there was initial evidence of renal impairment, the patients were continued on this same program after the time of discharge from the hospital. If signs of sodium depletion developed while under observation, the diet was changed to an 800 mg. sodium intake or to an even higher amount, if clinical judgment indicated. Each patient was given choline and supplementary vitamins orally in addition to the diet.

Since patients with ascites are in electrolyte balance, restriction of sodium alone will prevent further accumulation of extracellular fluid but will not produce significant loss of fluid already accumulated. Ammonium chloride and mercurial diuretics were therefore used in addition to sodium restriction to promote diuresis of previously retained sodium and its accompanying

* Supplied by Mead Johnson and Co., Evansville, Indiana.

water. If this was accomplished, paracentesis and its associated protein loss could be avoided. In several instances it was recognized that the discomfort from distention and the associated anorexia prevented adequate dietary intake. Paracentesis was performed in such patients, and it was thought in these cases that prevention of the re-accumulation of fluid was of importance equal to the initial diuresis of the ascitic fluid.

RESULTS

Eight patients were treated with this régime. All could be classified as having far advanced portal cirrhosis of the liver. Many had small financial means.

CASE REPORTS

Case 1. A 49 year old male had noted symptoms for one year and ascites for one month. Abdominal paracentesis had never been performed. The liver was small and not palpable. On his first admission there was an 18 pound (8.2 kg.) weight loss, with complete disappearance of ascites in 17 days. Following discharge he did not re-accumulate ascitic fluid and gained only five pounds (2.3 kg.) in weight over a 50 day period. He abandoned the diet for economic reasons, and there was a prompt gain in weight and return of ascites. Again, following hospitalization and return to the régime, he lost 15 pounds (6.8 kg.), with disappearance of the ascites in the next 30 days. Subsequent examinations have shown him clinically and subjectively improved, but repeated liver function studies have revealed no significant change. His spleen has become palpable.

Case 2. A 60 year old male clerical worker gave a history of abdominal distention of four months' duration which had required a single abdominal paracentesis of 6 L. of fluid. Examination revealed marked ascites and edema of the lower legs. The liver was never palpable. The patient lost 19 pounds (8.6 kg.) during 15 days of hospitalization, and his ascites was markedly diminished but remained present. A paracentesis of 5,000 c.c. of fluid was performed to facilitate discharge. He followed the diet well at home, and his weight remained stationary for one month. He returned to work. Ten weeks following hospitalization a massive hematemesis occurred, requiring the administration of blood and saline at his local hospital. He was transferred to the University Hospital with massive ascites and marked generalized wasting. Paracentesis of 4,500 c.c. was done, following which his weight remained stable on the régime. Because of the previous severe hematemesis and the relatively good values of liver function studies, the patient was transferred to the surgical service for a lienorenal anastomosis and splenectomy. His postoperative course was stormy, and death occurred on the twenty-fourth postoperative day following multiple massive hematemeses. Postmortem examination revealed a cirrhotic liver weighing 1,150 gm.

Case 3. A 68 year old male gave a history of exertional dyspnea and ankle edema of several years' duration and abdominal distention for one year. Previous abdominal paracenteses had been performed at monthly intervals for several months, with removal of 9,600 to 14,500 c.c. of fluid at each tap. Examination revealed marked ascites. Hepatomegaly was demonstrated after removal of the ascitic fluid, which had been done following admission to relieve dyspnea and anorexia. On the standard régime he lost an additional six pounds (2.8 kg.) during the next 22 days, with no re-accumulation of his ascites or edema. This was his longest period without ascitic fluid for the past year. Following discharge he failed to adhere to the diet and resumed his alcoholism. A paracentesis was performed elsewhere two

months later, with removal of 8,000 c.c. of fluid, and at this hospital one month thereafter with removal of 5,600 c.c.

Case 4. An indigent male of 64 years complained of cough, abdominal swelling and ankle edema of two months' duration. Three previous paracenteses had been performed elsewhere. Examination revealed a left pleural effusion, massive ascites and ankle edema. Hepatomegaly was noted after removal of ascitic fluid. Following hospitalization a thoracentesis (1,200 c.c.) and an abdominal paracentesis (9,300 c.c.) were performed, with symptomatic relief. On our standard régime he lost an additional nine pounds (4.1 kg.) in six days. His weight remained stabilized for the next eight days. On the eighth day he became weak, lethargic and mentally confused. Blood chemistry studies at this time revealed a non-protein-nitrogen of 56 mg. per cent, CO_2 combining power of 39 vol. per cent, and a plasma chloride of 100 mEq. per liter. (The patient had been receiving ammonium chloride.) He was placed on an unrestricted sodium diet and given 500 c.c. of physiologic saline solution intravenously, with prompt relief of his symptoms, which were attributed to sodium depletion. This resulted in a six pound (2.8 kg.) weight gain in two days. He was placed on a diet containing approximately 800 mg. of sodium per day, with a subsequent weight reduction of three pounds (1.4 kg.) and weight stabilization thereafter for the remainder of his hospitalization. Examination three months later revealed that he had abandoned the diet, and his ascites had returned.

Case 5. A 60 year old male had had many previous hospitalizations for chronic pyelonephritis, nephrolithiasis and multiple papillomas of the bladder. A right nephrectomy had been performed in 1946 and a fulguration of the papillomas in March, 1949. The tissue from the bladder was reported as showing early adenocarcinoma. His admission to the medical service was precipitated by abdominal distention and ankle edema of two weeks' duration. An abdominal paracentesis of 1,000 c.c. of fluid had been performed two weeks prior to admission. On a diet unrestricted in salt the patient gained three pounds (1.4 kg.) in three days, with an increase in his abdominal fluid. In spite of his renal impairment he was placed on the standard regimen and lost eight pounds (3.6 kg.) in 12 days. On the fifteenth hospital day he developed lethargy, weakness and mental confusion, associated with a rise in the non-protein-nitrogen to 62 mg. per cent. He was placed on a diet containing 40 gm. of protein and unrestricted in sodium. The symptoms attributed to sodium depletion cleared promptly, and the non-protein-nitrogen fell to 32 mg. per cent. During the three days of unrestricted sodium intake he gained seven pounds (3.2 kg.) and had a return of his ascites. Following an abdominal paracentesis of 4,700 c.c. he was placed on a diet containing 800 mg. of sodium. His weight stabilized and he was discharged. He remained free of ascites on this program until death occurred three months later, due to carcinomatous obstruction of the remaining ureteral orifice. At autopsy his liver weighed 1,450 gm. and revealed atrophic cirrhosis and no evidence of metastatic carcinoma.

Case 6. A 46 year old male gave a history of ascites of six months' duration. At another hospital he had been prescribed a "low salt diet" and diuretics, but despite this program had required three abdominal paracenteses prior to admission to University Hospital. On the day following admission, abdominal paracentesis of 5,780 c.c. was done and the standard régime instituted. On the third day he became mentally confused, restless and incontinent of urine. In spite of rigid sodium restriction he progressively gained weight and had a return of his ascites. There was no response to diuretics. On the twelfth hospital day, just prior to death, the non-protein-nitrogen had risen to 62 mg. per cent, the plasma chlorides were 92 mEq./L. (he was receiving ammonium chloride), and the serum sodium was 103 mEq./L. Postmortem examination revealed advanced atrophic cirrhosis, with a liver weighing 1,515 gm.

Case 7. A 42 year old male complained of abdominal distention for the past six months and scrotal and leg edema for the past three months. He had had two previous paracenteses. On the standard régime the patient lost 29 pounds (13.2 kg.) in one month and became free of ascites and edema. This was accompanied by clinical improvement and a slight rise in the total serum proteins; the albumin fraction rose to 2.9 per cent. He was then placed on a diet unrestricted in sodium and gained only three pounds (1.4 kg.) in nine days.

Case 8. A 55 year old housewife had been known to have cirrhosis for 18 months and had required alternating abdominal paracenteses and mercurial diuretics at weekly intervals for the past six months. A paracentesis of 4,400 c.c. of fluid was performed the day following admission. On the standard régime she lost an additional five pounds (2.3 kg.) in 15 days, and her weight remained stationary for the next 40 days. Administration of a diet unrestricted in sodium resulted in a nine pound (4.1 kg.) gain in weight in four days. Sodium restriction was re-instituted. During the period she improved clinically, with a slight rise in the total serum proteins and the albumin fraction and a fall in the globulin fraction.

To summarize: In seven of the eight cases, prevention and retardation of the formation of ascites were accomplished. In case 1, weight was reduced 18 pounds (8.2 kg.) in a period of 17 days with disappearance of ascites. Ascitic fluid did not re-accumulate until the diet was abandoned; abdominal paracentesis was never required. Cases 2, 3, 4, 5, 7 and 8 were patients who had required one or more abdominal paracenteses prior to hospitalization. In some of these cases, the ascitic fluid volume could not be reduced rapidly enough by sodium restriction and diuresis, and a paracentesis was performed after hospitalization. Significant re-accumulation of ascitic fluid in all these patients was prevented by sodium restriction. Failure to follow the régime resulted in return of ascites in each case but one (case 7).

Despite sodium restriction and the use of diuretics, one patient (case 6) continued to form ascitic fluid, with resultant dilution of his extracellular electrolytes and ultimate death. Twenty-four hours prior to death his serum sodium was diluted to 103 mEq. per liter. If 15 L. is accepted as the average normal total volume of extracellular fluid, a dilution of the serum sodium concentration by approximately one-third (140 mEq. per liter to 103 mEq. per liter) would indicate an increase in extracellular fluid to about 20 L. Approximately 5 L. of ascitic fluid were found in the peritoneal cavity at postmortem examination. Some time during their hospitalization, cases 4 and 5 exhibited symptoms that were relieved by sodium administration and, although serum sodium concentrations were not reported, it was assumed that they suffered sodium depletion. In these cases, re-accumulation of ascitic fluid was prevented by less drastic sodium restriction.

DISCUSSION

The three recognized factors contributing to the formation of ascites in cirrhosis of the liver are (1) portal hypertension, (2) depleted serum proteins, particularly hypoalbuminemia, and (3) the retention of water and

sodium* attributed to hormonal or humoral influence on the renal tubules.^{4, 5} The problem of portal hypertension has been attacked mechanically, but these patients are notoriously poor operative risks, the procedures are technically difficult, and even with apparent relief of the hypertension there is frequently no significant reduction in the formation of ascites. The hypoalbuminemia can be rapidly corrected only by the frequent and continued intravenous administration of salt-poor serum albumin. The expense of this procedure is prohibitive and the method is not without hazard. Furthermore, Ralli and co-workers⁴ concluded that the level of the serum albumin in the plasma was not the determining factor in fluid retention but rather that an antidiuretic factor was of primary importance. This leaves, as the third avenue of therapeutic approach to this complication, the restriction of sodium intake as a means of retarding and preventing re-accumulation of ascitic fluid.

The work of McKee, Whipple, and associates⁶ in experimental ascites showed that the formation of ascites constituted a protein loss to the organism comparable to plasmapheresis, and that a high protein diet low in sodium resulted in a minimal ascitic fluid accumulation. Farnsworth,⁷ Eisenmenger and associates⁸ and others have confirmed that urinary excretion of sodium is extremely low in patients with cirrhosis. Nevertheless, we believe that sodium excretion in the urine is indirectly proportional to the rate of accumulation of extracellular fluid and that it will vary according to the stage of the disease.

The availability of low-sodium protein supplements makes it possible to insure a high protein intake with accompanying rigid sodium restriction as a means of meeting these requirements. It is of interest to note that patients were in nitrogen balance on the dietary intake of approximately 58 gm. of protein allowed in our 200 mg. sodium diet without the addition of protein supplements. In some instances, less drastic sodium restriction was sufficient, in agreement with findings of Layne and Schemm,⁹ Eisenmenger, et al.⁸ and Sterling, et al.¹⁰ Other patients, however, had a return of fluid accumulation with liberalization of the sodium intake.

Rigid sodium restriction is not without hazard. Even with no evidence of previous impairment of renal function, it is possible for these patients to dilute their electrolytes and develop a "low sodium syndrome." In contrast to the "low sodium syndrome" seen in renal impairment and other conditions, these patients did not develop signs of dehydration and hypotension. They did exhibit lethargy, mental confusion, nitrogen retention and failure to develop diuresis. In these individuals sodium administration is indicated, and it is still possible to adjust the sodium intake so that re-accumulation of extracellular fluid is retarded. If estimations of serum sodium are not readily available, it is thought that close surveillance and

* Information now available indicates that the retention of water requires retention of a specified amount of sodium, or the extracellular electrolytes will become diluted, with resulting death of the organism.

clinical judgment must be exercised as a means of recognizing sodium depletion. Unless the patient has lost the ability to maintain electrolyte balance, there can be no re-accumulation of extracellular fluid without its equivalent of sodium, and if sodium is not presented for retention, ascitic fluid cannot accumulate. We have no idea how frequently the loss of ability to maintain electrolyte balance occurs, but we have seen it only in terminal stages.

We have not lost sight of the fact that the primary problem is extensive liver damage and that ascites is merely a troublesome complication. The importance of an adequate protein, carbohydrate and vitamin intake in the management of cirrhosis has been stressed repeatedly in the literature. This means that any dietary régime must be sufficiently palatable to be eaten by patients with a capricious appetite. We have found that, with care in preparation, this diet is palatable, and there have been few complaints once the patients have forgotten their taste for salt. No comment can be made at this time on the effect of this régime upon the ultimate prognosis of cirrhosis, for the period of observation of the cases has been insufficient. None has been followed for more than a year. It is considered that the low sodium regimen, with its recognized limitations, is logical and worthwhile in the management of decompensated cirrhosis of the liver. The patient can be spared the necessity and discomfort of frequent abdominal paracenteses with the accompanying serious loss of serum protein.

SUMMARY

1. An evaluation of rigid dietary sodium restriction as a means of preventing re-accumulation of ascitic fluid was made in eight cases of far advanced cirrhosis of the liver.
2. With the use of low-sodium protein supplements, it was possible to give a diet high in protein, carbohydrate and calories.
3. Since under ordinary conditions 150 mg. of sodium are lost in the stool and in sweat per 24 hours, only 50 mg. (2.2 mEq.) of sodium will be available for urinary excretion or for retention by the organism if the daily sodium intake is limited to 200 mg. Since 1 L. of extracellular fluid contains approximately 140 mEq. of sodium, even if 2.2 mEq. of sodium were retained daily (which implies a sodium free urine), 64 days would be required to accumulate 1 L. of extracellular fluid, provided the power of maintaining a normal electrolyte balance is retained.
4. Rigid sodium restriction is not without hazard. Close clinical surveillance is necessary to guard against the serious complication of sodium depletion. If sodium depletion develops, electrolytes should be replaced even if this results in the formation of ascites.
5. Since sodium restriction spares the patient with hepatic cirrhosis with ascites serious protein loss and the discomfort of frequent abdominal paracentesis, it is considered worthwhile.

Acknowledgment. We gratefully acknowledge the inspiration and advice of Dr. L. H. Newburgh in the encouragement of this study.

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NITROGEN BALANCE STUDIES IN LAENNEC'S CIRRHOSIS OF THE LIVER*

By WALTER R. COOK, COLONEL, M. C., U. S. Army, F.A.C.P., and
HOWARD A. VAN AUKEN, COLONEL, M. C., U. S. Army, F.A.C.P.,
Fort Sam Houston, Texas

LAENNEC'S cirrhosis, the most common type of cirrhotic involvement of the liver, has also been called atrophic or hypertrophic cirrhosis, hobnail cirrhosis, alcoholic cirrhosis and even "gin-drinker's liver." Pathologically, this disease is characterized by an increase in portal connective tissue with the production of dense fibrous bands, degenerative changes in the parenchymal cells, dissociation of hepatic cords and variable degrees of regeneration and fatty and cellular infiltration. It is generally agreed that necrosis of the parenchymal cells precedes the overgrowth of the fibrous tissue. Complications resulting from this hepatic disease are: obstruction of the portal venous channels leading to esophageal varicosities, abdominal ascites, congestion of the mesenteric veins, and the development of a collateral circulation with congestion of the abdominal wall. While Laennec's cirrhosis is found in about 3 per cent of all postmortem examinations in this country, it has recently been claimed that this affliction is definitely on the increase.

The causes of portal cirrhosis are obscure. A great majority of the cases give a history of chronic alcoholism. Preëxisting infectious hepatitis is elicited in the past history of some 5 to 10 per cent of the cases of Laennec's cirrhosis, but it is difficult definitely to incriminate this viral illness as the direct etiologic agent. Recently nutritional deficiency has been related to the production of cirrhosis, not only because of the frequent association of alcoholism and poor dietary intake, but also because of the favorable therapeutic response to an adequate diet. Some authorities still cling to alcohol as having a direct toxic action on the liver, but it is more generally believed that dietary deficiency is the predominant cause, and that excessive alcohol interferes with proper eating and tends to increase liver injuries so produced. The heavy metals, including arsenic and phosphorus, and carbon tetrachloride have been incriminated in occasional cases of portal cirrhosis, but the relationship is not at all clear.

The treatment of Laennec's cirrhosis in recent years has been much improved. Whereas formerly the disorder progressed relentlessly to a fatal termination, it is now known that a high protein, high vitamin diet, supplemented liberally by choline, methionine and/or cystine, may not only arrest the progress of the disease but actually reverse the trend and bring about at least a partial cure. In the many papers reporting the remarkably improved

* Received for publication September 25, 1950.
From Brooke Army Hospital, Fort Sam Houston, Texas.

results in this disease, little attention has been given to nitrogen balance in the treated patients; in fact, nowhere in the literature have we been able to find detailed studies of this phase of the treatment of Laennec's cirrhosis of the liver.

It is the purpose of this paper to study the course of cases of Laennec's cirrhosis of the liver treated with an intensive combined therapy, with particular reference to nitrogen metabolism. The type of treatment of the patients studied is essentially that recommended by Lester M. Morrison,¹ as follows: (1) Basic diet, 2,500 to 4,000 calories; 150 to 250 gm. protein, 300 to 500 gm. carbohydrate, 50 to 100 gm. fat. (2) Liver extract and vitamins: Intraheptol (Lederle's liver concentrate), administered intravenously in distilled water, beginning with 0.5 c.c. daily and gradually increasing to 6 c.c. two to three times weekly. The liver extract is reinforced intravenously with Solu B (B complex) and multi-vitamins orally. (3) Specific agents: 2 gm. methionine and 2 gm. choline orally daily; casein and cysteine supplied by high intake of skimmed milk and cottage cheese daily.

Diets were prepared by dietitians who computed all values and measured all refusals of food. It is a known fact that there is a maximum of 10 per cent variation between values for nitrogen calculated from tables and values actually determined by analysis of food, but these values tend to cancel out

TABLE I

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Control Case 1							
Mar. 13, 1950	100	16	2,090	13.2	280	2.7	+0.1
Mar. 14, 1950	100	16	1,440	10.8	242	2.1	+3.1
Mar. 15, 1950	100	16	2,440	23.0	67	1.0	-8.0
Mar. 16, 1950	100	16	1,590	14.1	117	.9	+1.0
4 days	400	64		61.1	706	6.7	-3.8/4 = -0.9 per day
Control Case 2							
Mar. 14, 1950	128	20.5	5,600	24.9	128	1.7	-6.1
Mar. 15, 1950	128	20.5	4,600	18.9	81	.6	+1.0
Mar. 16, 1950	128	20.5	4,000	21.5	117	.9	-1.9
3 days	384	61.5		65.3	326	3.2	-7.0/3 = -2.3 per day
Control Case 3							
Mar. 13, 1950	94	15.0	1,125	13.8	62	.6	+0.6
Mar. 14, 1950	93	14.8	1,800	16.7	23	.6	-2.5
Mar. 15, 1950	100	16.0	1,950	12.2	366	2.8	+1.0
Mar. 16, 1950	94	15.0	1,000	11.5	195	.9	+2.6
4 days	381	60.8		54.2	569	4.9	+1.7/4 = +.4 per day

in the long view. The value for proteins in grams was divided by 6.25 to determine the weight of the nitrogen in grams in the food.

Laboratory determination of the nitrogen excreted in the urine and feces, when compared with the dietary intake, established the nitrogen balance in each individual. The loss of nitrogen in the breath and perspiration was considered to be negligible in these patients. Other laboratory work included the usual routine blood counts, urinalyses and liver function tests to establish the diagnosis and evaluate the results of therapy.

Urinary and fecal nitrogen were determined by the Kjeldahl method. Bromsulfalein retention was determined 45 minutes after administration of 5 mg. of the dye per kilogram of body weight. Thymol turbidity was determined by the modification of Shank and Hoagland; serum bilirubin, by the method of Evelyn and Malloy; cholesterol and cholesterol esters, by a modified Bloor procedure; albumin, globulin and total protein, by the method of Kingsley; and cephalin cholesterol flocculation, by the method of Hangar.

Nitrogen balance studies were initially carried out for four days on three control cases in the hospital to determine the accuracy of the procedures. The first case was a well controlled diabetic on a 2,000 calorie diet containing 100 gm. protein daily. The second case was a well controlled diabetic on a 2,800 calorie diet containing 128 gm. protein daily. The third case was one of moderate hypertension who was maintained on a weighed diet during the test period. The results are presented in table 1. They show these patients to be in nitrogen balance and indicate that the procedures used in this study were accurate.

CASE REPORTS

Case 1. A 55 year old white male entered the hospital with a history of excessive intake of alcohol for eight years and poor appetite at intervals lasting for three months. He had been averaging several bottles of beer and a half-pint of whiskey for many years. For the past five years the patient had ignored the advice of physicians to curtail his alcohol intake. During the past year he noticed that his urine had been dark at times. His stools were usually of normal color, although occasionally they were black. Two months prior to admission he noticed that his eyes were yellow and that his skin had a slight icteric tinge. Just before admission he complained of distention of the abdomen, and stated that his trousers no longer fitted him at the waist.

On physical examination he was emaciated and appeared acutely and chronically ill. The sclerae were icteric. The liver was enlarged and nodular, and ascites was present. The skin showed many spider angiomas. He was mildly anemic. There was moderate pitting pretibial edema. The urine was positive for bile. The icterus index was 24, serum bilirubin 8.8 mg., thymol turbidity 7.8, bromsulfalein retention 44 per cent. It was at first difficult to induce the patient to take nourishment voluntarily, but gradually the Morrison régime was instituted. Periodically he received human serum albumin intravenously. His mental status cleared gradually over many months, although his clinical jaundice, ankle edema and abnormal liver function tests persisted. His abdominal ascites cleared up and did not return. During his six months' hospitalization the patient was detected on several occasions consuming alcoholic beverages. He finally insisted on being discharged against medical advice.

symptomatically improved but still showing definite evidence of poor liver function, including a bromsulfalein retention of 32 per cent. Nitrogen balance studies are shown in table 2.

Comment: This patient showed many poor prognostic signs, namely, persistent jaundice, ankle edema, clouding of the sensorium and markedly abnormal liver function tests. Persistent alcoholic intake probably was a factor in continuing his poor response to treatment. The nitrogen balance studies on a high protein intake indicated a severe degree of protein depletion, as manifested by a strongly positive nitrogen balance, except for one day when his dietary intake was extremely low. Whenever sufficient protein was ingested, there was always a positive nitrogen balance. Even though treated with a high protein diet for almost a year he still showed evidence of storing large amounts of nitrogen.

Case 2. A 64 year old white male entered the hospital complaining of progressive distention of the abdomen. He had lost a great deal of weight during the last six months, and he had had his abdomen drained once prior to entering the hospital. Fluid had, however, re-accumulated. He gave a history of a very poor

TABLE II

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Dec. 20, 1949	139	22.2	1,300	13.9	72	.8	+7.5
Dec. 21, 1949	55	8.9	1,500	13.0	229	2.5	-6.6
Dec. 22, 1949	139	22.2	1,520	17.8	143	1.3	+3.3
Dec. 23, 1949	146	23.4	1,350	14.6	204	2.4	+6.4
Jan. 9, 1950	196	31.6	1,275	10.7	131	1.4	+19.5
Jan. 10, 1950	197	31.8	1,150	11.6	310	4.4	+15.8
Jan. 11, 1950	196	31.6	1,175	13.4	353	3.8	+14.4
Jan. 12, 1950	207	33.5	1,185	12.2	173	2.2	+19.1

dietary intake because his ill-fitting teeth made it impossible for him to chew. He had been living on practically nothing but milk. Ten years previously he had suffered a fractured right thigh which had not healed properly and caused considerable difficulty in walking. He gave a negative alcoholic history.

Laboratory examination showed bromsulfalein retention of 18 per cent, a moderate reduction in total protein with an A/G ratio of 1.1 and a positive cephalin flocculation reaction. Other examinations were essentially normal. During his hospitalization he was placed on the Morrison type of treatment, to which he responded very satisfactorily. His false teeth were repaired so that he was able to chew his food adequately. On a high protein diet and other therapy there was no re-accumulation of ascitic fluid. The bromsulfalein retention dropped to 10 per cent and his total protein came up to normal. Nitrogen balance studies are shown in table 3.

Comment: The markedly positive nitrogen balance is again evidence of severe protein depletion, presumably brought about over a long period of time. This observation was made after the patient had been on therapy for almost a year, during which time he consumed what was considered an adequate diet. It again indicates the severe protein depletion in an individual suffering from cirrhosis of the liver.

TABLE III

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Jan. 4, 1950	59	9.4	1,350	10.0	13	.2	-.8
Jan. 5, 1950	159	25.5	1,800	9.7	—	—	+15.8
Jan. 9, 1950	174	28.1	950	8.5	323	3.1	+16.5
Jan. 10, 1950	163	26.3	1,650	9.7	101	1.5	+15.1
Jan. 11, 1950	195	31.6	600	4.8	—	—	+26.6
Jan. 12, 1950	127	20.6	1,000	13.4	220	2.2	+5.0
Jan. 22, 1950	189	30.4	900	5.9	222	1.8	+22.7
Jan. 23, 1950	162	26.0	1,550	11.2	87	1.0	+13.8
Jan. 24, 1950	160	25.7	1,000	7.7	39	.4	+17.6
Jan. 25, 1950	150	23.9	1,000	6.5	270	4.6	+12.8
Jan. 26, 1950	159	25.4	750	5.9	166	1.7	+17.8

Case 3. This patient had been well until August, 1948, when it was noted that his skin was yellow. Five months prior to this time he had noticed anorexia and a loss of about 10 pounds in weight. While hospitalized he developed ascites, and a paracentesis had to be done. His icterus index was high, and there was a low total protein. Following the diagnosis of cirrhosis of the liver, he was transferred to Brooke General Hospital, somewhat improved. In 1926 he had been treated for syphilis, being given what was considered adequate treatment at that time.

Physical examination showed a distended abdomen with a fluid wave and slight tenderness in the right upper quadrant. There were numerous spider angiomas scattered over the upper portion of the trunk. Following paracentesis, the liver was found to be moderately enlarged. Serum bilirubin was 2.2 mg.; thymol turbidity, 3.4; bromsulfalein retention, 25 per cent; total protein, 5.3 gm.; albumin, 3.3; globulin, 1.5. Serologic examination, including spinal fluid, was negative.

Patient was put on the Morrison régime and showed steady improvement in his disease. Paracentesis did not have to be repeated and the liver began to decrease in size. The patient was discharged from the hospital but did not follow advice as to diet and abstinence from alcohol. He was again admitted in August, 1949, and an abdominal paracentesis was done, yielding 9,200 c.c. of fluid. He was again placed on the Morrison régime, but repeated paracenteses were necessary, although the intervals between taps became longer. Nitrogen balance studies are shown in table 4.

Comment: This patient's symptoms attributable to liver disease had been present for at least two years, and there was a long history of alcoholism. He initially made a satisfactory response to treatment but continued his

TABLE IV

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Dec. 20, 1949	135	21.6	1,650	11.8	148	1.4	+8.4
Dec. 21, 1949	60	9.6	1,550	10.3	182	2.4	- 3.1
Dec. 22, 1949	160	25.6	1,140	16.7	112	1.7	+ 7.2
Jan. 4, 1950	158	25.3	1,020	9.1	118	1.9	+14.3
Jan. 5, 1950	188	30.1	930	7.6	223	2.3	+20.2
Jan. 9, 1950	194	31.3	910	10.8	232	1.5	+19.0
Jan. 10, 1950	171	27.6	1,020	10.2	158	1.6	+15.8
Jan. 11, 1950	176	28.5	1,130	10.0	239	2.3	+16.2
Jan. 12, 1950	192	30.9	1,260	10.3	173	1.9	+18.7

alcoholic consumption and poor dietary intake after discharge from the hospital. He continued to accumulate abdominal fluid, although with some improvement in his condition. The nitrogen studies on a high protein intake indicated chronic protein depletion, and in spite of months of treatment he still showed nitrogen depletion. Undoubtedly, some nitrogen was lost in the abdominal fluid that periodically had to be aspirated. Analysis of the ascitic fluid removed during one 13 day period showed a daily loss of 2 gm. nitrogen in the fluid. Even if this were deducted from the nitrogen retained, the patient would still be adding to his body protein when on appropriate therapy.

Case 4. A 43 year old white male first had symptoms of peptic ulcer in 1947, for which a subtotal gastric resection was done. He got along fairly well on medical treatment, but during the fall and winter months of 1949 there was a history of alcoholic excess and very irregular eating. In October he began to tire easily and

TABLE V

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Jan. 9, 1950	143	23.1	800	2.8	300	4.8	+18.5
Jan. 10, 1950	125	20.2	700	4.9	157	2.6	+12.7
Jan. 11, 1950	144	23.1	300	1.8	—	—	+21.3
Jan. 12, 1950	167	26.9	400	17.6	—	—	+ 9.3
Jan. 15, 1950	139	22.4	1,400	10.3	140	2.7	+ 9.4
Jan. 16, 1950	146	23.4	1,500	5.5	275	2.8	+15.1
Jan. 17, 1950	180	29.0	1,000	4.5	532	4.6	+19.9
Jan. 18, 1950	171	27.6	1,400	8.2	339	5.3	+14.1
Jan. 19, 1950	172	27.8	1,800	10.9	379	4.9	+12.0
Jan. 22, 1950	152	24.4	900	5.2	318	2.9	+16.3
Jan. 23, 1950	134	21.4	900	4.9	347	5.2	+11.3
Jan. 24, 1950	138	22.1	700	3.5	510	6.6	+12.0
Jan. 25, 1950	121	19.3	1,350	12.6	346	2.2	+ 4.5
Jan. 26, 1950	103	16.4	1,000	3.6	366	5.8	+ 7.0
Mar. 13, 1950	46	7.3	1,800	25.6	169	1.1	-19.4
Mar. 14, 1950	90	14.4	1,025	5.2	80	1.3	+ 7.9

to lose his appetite. On one occasion he vomited coffee-ground material. Later his urine became scanty and dark, and on November 19, 1949, clinical jaundice was noted. This was followed by soft stools, ankle edema, abdominal distention and nose bleeds. Paracentesis of the abdomen was necessary. On transfer to Brooke General Hospital there were noted marked loss of weight, emaciation, senile appearance, jaundice, abdominal ascites, dilatation of the surface vessels of the upper abdomen, an enlarged firm liver and scattered spider angiomas over the upper chest and neck. The bromsulfalein retention was 36 per cent; thymol turbidity, 5.2 units; serum bilirubin, 19 mg. The total protein was 7.8 gm., of which 3.8 was albumin and 4.0 globulin.

While in the hospital, he initially had frequent loose bowel movements, frequent nose bleeds and evident mental depression. He had difficulty accepting the Morrison régime but finally did so, with a gain in weight and a recession in the degree of jaundice. There was considerable improvement in his liver function studies, the bromsulfalein dropping to 10 to 12 per cent retention. Nitrogen balance studies are shown in table 5.

Comment: The very low values of urinary nitrogen excretion indicated severe protein depletion. The patient demonstrated the loose, frequent bowel movements so often seen early in the course of Laennec's cirrhosis. The fecal nitrogen was persistently elevated, and it is believed that this was due to a combination of hyperperistalsis and edema of the intestinal mucosa with accompanying surface inflammation. Despite the fact that he was under treatment with a high protein diet for almost four months, he still showed evidences of chronic protein depletion, although the degree of positive balance was decreasing. Very early, there was reversal of the A/G ratio, but this was rapidly corrected on the Morrison régime. The thymol turbidity test gave little evidence of the clinically severe liver disease.

Case 5. A 54 year old white male was admitted to Brooke General Hospital with the chief complaints of dyspnea, insomnia, pain under the ribs on the right side, cough and easy fatigability, along with irritability. There was a history of repeated respiratory infections in the recent past. For many years he had been a heavy drinker. Physical examination showed muddiness of the sclerae but not definite icterus. There was prominence of the breasts bilaterally (gynecomastia). The

TABLE VI

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Jan. 22, 1950	159	25.4	1,200	9.5	124	1.0	+14.9
Jan. 23, 1950	169	27.1	2,200	10.8	92	1.0	+15.3
Jan. 24, 1950	147	23.5	1,100	8.5	410	4.7	+10.3
Jan. 25, 1950	162	25.9	1,550	12.4	144	1.1	+12.4
Jan. 26, 1950	103	16.5	1,400	11.6	336	3.7	+ 1.2
Jan. 30, 1950	100	16.0	1,350	22.1	167	1.3	- 7.4
Jan. 31, 1950	142	22.7	1,900	9.8	332	2.7	+10.2
Feb. 1, 1950	144	22.9	2,000	12.8	—	—	+10.1

liver was enlarged four fingerbreadths below the right costal margin and was much firmer than normal. There were many spider angiomas over the face, back, shoulders and upper chest. His bromsulfalein retention was 36 per cent; serum bilirubin, 0.8 mg.; thymol turbidity, 4.4; total protein, 7.8, of which 4.5 was albumin and 3.3 globulin.

The patient was very irritable and, although desiring to get well, at times was unwilling to coöperate in accepting the high protein, high carbohydrate diet of the Morrison régime. He complained bitterly of pain in the feet and legs, which was believed to be the result of a malnutrition type of peripheral neuritis. When he finally was induced to take the Morrison régime, he showed clinical improvement. Nitrogen balance studies are shown in table 6.

Comment: This case represented a severe alcoholic of long standing. Nitrogen studies showed evidence of severe protein deficiency. He had loose bowel movements with increased fecal nitrogen content, as many cirrhotics show early in the course of their high protein dietary treatment. Because of the irritability and uncoöperative attitude of the patient, further nitrogen studies were not carried out. This case illustrated further some of the psychiatric aspects of the illness.

Case 6. A 57 year old white male was admitted to the hospital because of an enlarged liver. There was a history of several years of excessive alcohol intake and a poor food intake. Physical examination showed the liver to be four to five fingerbreadths below the right costal margin, smooth and hard but not nodular. Several small spider angiomas were seen over the upper chest. The bromsulfalein retention shortly after admission was 23 per cent. There was no clinical jaundice, and the icterus index was not elevated. The prothrombin time was normal. The patient was placed on a Morrison régime for cirrhosis of the liver, and alcoholic intake was completely stopped. At no time was any ascites found. He was discharged from the hospital with recommendation to continue the high protein diet and other measures.

Six months later the patient was re-admitted to the hospital for follow-up of his hepatic condition. He felt quite well and stated he had followed his treatment faithfully and had totally abstained from alcohol. The liver was possibly slightly smaller but was still firm and smooth. The spleen was not felt. The bromsulfalein retention had fallen to 12 per cent. Nitrogen balance studies carried out at this time are shown in table 7.

TABLE VII

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Jan. 30, 1950	196	31.4	1,300	10.2	148	1.7	+19.5
Jan. 31, 1950	172	27.6	1,000	23.2	118	1.2	+ 3.2
Feb. 1, 1950	188	30.1	2,600	20.4	149	1.5	+ 8.2
Feb. 2, 1950	192	30.7	3,000	37.4	187	2.6	- 9.3

Comment: Nitrogen studies after eight months of treatment showed a moderate positive balance, indicating that protein was still being stored and that, despite prolonged therapy, the patient had not yet returned to complete nitrogen equilibrium.

Case 7. A 66 year old white male was admitted to the hospital complaining of having had chills and fever for the past two days. The chills were shaking in nature, lasted about 30 minutes and were followed by a fever of 102° F. The patient also stated he had not felt well for the last two months, during which time there had been intolerance to all foods and excessive abdominal distention and gas. For two days prior to admission he had noted progressively darker urine, clay-colored stools and a slight pain in the right upper quadrant. He stated that at times he had drunk excessively and in the past several years had not eaten very well. He had had a cholecystectomy in 1947. Physical examination showed deep clinical jaundice. The liver was enlarged four fingerbreadths below the right costal margin and was slightly tender and firm but not nodular. At the time of entry there was a 2 plus albumin in the urine, which was loaded with white blood cells and positive for bile. The icterus index was 20; bromsulfalein retention was 21 per cent; serum bilirubin was 4.2 mg.; thymol turbidity was 15 units; cephalin flocculation showed a trace at 48 hours. A biopsy of the liver showed Laennec's cirrhosis.

The chills and fever continued for approximately two weeks, during which time he was given penicillin, streptomycin and two blood transfusions. He was then placed on the Morrison régime. The jaundice gradually subsided, and he was discharged from the hospital without evidence of icterus. He was advised to continue on the Morrison régime and to abstain from alcohol.

Nine months later he was re-admitted for evaluation. He stated that he felt quite well, had adhered faithfully to his treatment and had totally abstained from alcohol. There was no clinical icterus; the liver felt about the same as on the previous admission. Nitrogen balance studies carried out at this time are shown in table 8.

TABLE VIII

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Jan. 30, 1950	179	28.7	3,000	18.1	166	1.7	+ 8.9
Jan. 31, 1950	156	25.0	2,400	16.6	237	1.9	+ 6.5
Feb. 1, 1950	177	28.4	2,700	17.4	289	3.7	+ 7.3
Feb. 2, 1950	178	28.5	2,500	19.6	—	—	+ 8.9

Comment: This case of Laennec's cirrhosis was confirmed by biopsy. The patient made a good response while faithfully following the recommended treatment. There was never any ascites, ankle edema or splenic enlargement. Nitrogen studies after nine months of intensive medical treatment showed that he was storing moderate amounts of nitrogen, indicating that he still was in protein depletion. The bromsulfalein retention during this period had dropped to 6 per cent.

Case 8. A 53 year old white male was admitted to the hospital complaining of nausea, loss of appetite, dark brown urine, yellowish eyeballs, hiccups and general debility. The patient had been retired from the service approximately a year previously because of hypertensive cardiovascular disease. His wife had died recently and since her death he had been drinking heavily. He had been a prisoner of war in the Philippine Islands from 1942 to 1945, during which time he had had recurrent malaria, dysentery, beriberi and severe malnutrition. Physical examination showed a somewhat obese, chronically ill white male with a markedly protuberant abdomen. There were a few spider angiomas on the cheeks. There was a mild icteric tinge of the skin and sclerae. There was 2 plus edema of the right leg up to the knee. Blood pressure was 200 mm. Hg systolic and 100 mm. diastolic. There was engorgement of the veins between the umbilicus and xiphoid. The liver was palpable five fingerbreadths below the right costal margin and was irregular in outline and slightly tender. Laboratory findings showed bromsulfalein retention of 26 per cent, positive cephalin flocculation, icterus index of 36 and bilirubin of 19 mg. The thymol turbidity was 18.4 units.

The patient was placed on the Morrison régime and remained in the hospital for three and one-half months, during which time bromsulfalein retention dropped to 20 per cent; icterus index was 6, thymol turbidity 5.6, and cephalin flocculation test was faintly positive. He continued on the Morrison régime outside the hospital, following it faithfully and abstaining totally from alcohol.

One and one-half years later he was re-admitted for follow-up study. He still tired easily but had no abdominal complaints. The liver was still felt approximately four fingerbreadths below the costal margin but was nontender. There was no jaundice. Nitrogen balance studies carried out on the patient at this time showed that he was in nitrogen balance; the results are given in table 9.

Comment: It is probable that during this patient's imprisonment by the Japanese, from 1942 to 1945, the severe malnutrition brought about changes

TABLE IX

Date	Diet Protein, gm.	Diet N, gm.	Urine Volume, c.c.	Urine N, gm.	Stool Weight, gm.	Stool N, gm.	Nitrogen Balance
Mar. 13, 1950	135	21.7	2,000	18.1	188	2.1	- 0.4
Mar. 14, 1950	130	20.8	1,350	16.0	366	2.7	+ 2.1
Mar. 15, 1950	124	19.8	1,800	15.3	23	.6	+ 3.9
Mar. 16, 1950	139	22.3	1,800	19.8	126	1.3	+ 1.2

in his liver. He was a very faithful patient, following carefully the medical régime outlined for him. Nitrogen studies after almost two years of intensive treatment showed him to be essentially in nitrogen balance. His bromsulfalein fell to as low as 7 per cent. He represents an excellent response to therapy.

DISCUSSION

This study of nitrogen balance in cases of Laennec's cirrhosis of the liver was carried out on patients who were under treatment with intensive combined medical therapy over various periods of time, from several months to almost two years. Of the eight cases studied, six had been severe alcoholics over long periods of time, and one had been a Japanese prisoner of war, following which he undoubtedly imbibed more than normally. The remaining case was an orthopedic cripple who had been a drug addict. He gave a history of poor food intake for from six months to one year before the onset of abdominal ascites.

That all of the patients demonstrated severe nitrogen depletion and a positive nitrogen balance under appropriate conditions of therapy is not surprising. Many patients with chronic wasting diseases, including those suffering from severe burns, Addison's disease, diabetes mellitus, thyrotoxicosis and, as recently shown by Sappington and Bockus,² chronic peptic ulcer and ulcerative colitis, are in negative nitrogen balance. The same might well be expected in patients suffering from cirrhosis of the liver, in view of the metabolic disturbance brought about by this severe liver disorder, the chronically wasted state of the patients, their generally long history of inadequate dietary intake, and their blood chemistry findings. Numerous observations in the past have, in fact, suggested this very thing.

The normal individual on an average diet maintains perfect equilibrium between the protein nitrogen intake and output. On the other hand, the cirrhotic patient loses nitrogen, not only as the result of a dietary intake insufficient to meet his daily needs, but also from the defective functioning of the liver, which may fail to utilize the amino acids effectively. There may also be a considerable loss of protein in ascitic fluid, particularly in the more advanced cases of the disease. All of the patients in this study showed severe protein depletion. Even after taking a high protein diet for many months, they still showed evidences of storing nitrogen. Furthermore, the fact that after some months of treatment many of the patients still showed a

protein deficit suggests that many cirrhotics, regardless of treatment, may never entirely correct their protein deficits, or may accomplish this only after extremely prolonged periods of therapy. This observation was also made by Sappington and Bockus,² studying cases of chronic idiopathic ulcerative colitis.

No correlation could be made between body weight gained and nitrogen storage. Most of the patients gained weight during the time they were in a positive nitrogen balance, but the gain in weight did not appear to be directly related to the quantity of nitrogen stored. There also appeared to be no correlation between the plasma proteins and the degree of protein deficit. One patient showed a reduction in total plasma protein with A/G reversal early in the illness. One showed a slight reduction in total plasma protein and normal A/G ratio. One case showed normal plasma protein and slight A/G reversal. With a high protein diet, all rapidly showed normal plasma proteins, which remained normal throughout treatment. Some observers have reported difficulty in correcting the plasma proteins by diet in cirrhosis of the liver. Failure to bring about improvement in the plasma proteins is undoubtedly associated with far advanced disease with marked hepatic failure, conditions not existing in this series of cases.

In general, tests of liver function tend to improve as nitrogen equilibrium is approached and clinical improvement occurs. There was, however, considerable variation in results with different tests and on different patients. The only test which was correlated with improvement in these patients was the bromsulfalein retention. It quite regularly dropped as improvement occurred and seemed to be a good indicator of the degree of liver function. While other tests generally returned to normal soon after therapy was instituted, this test continued to show some degree of impairment of function. Nor did the status of the liver function tests show any close correlation with the ability of the patient to assimilate nitrogen and go into positive balance. It is probable that the fact that none of the patients was in the last stages of the disease accounts in part for the lack of correlation between the liver function studies and improvement of the patients.

SUMMARY

Eight cases of Laennec's cirrhosis of the liver were treated with intensive combined medical therapy for periods of from three months to almost two years. Six of the cases were alcoholics, one was a former Japanese prisoner of war, and the remaining case was an orthopedic cripple who had been a drug addict. Seven of the eight cases showed clinical and laboratory evidence of improvement. The case that was a clinical failure persisted in the use of alcohol and in failing to follow treatment.

All of the patients went into positive nitrogen balance when placed on suitable therapy and diet. Only one of the cases under treatment for a

period of almost two years reached apparent nitrogen equilibrium. The others, after months of therapy, still showed evidence of storing nitrogen.

The suggestion was drawn from these studies that patients with Laennec's cirrhosis of the liver may never regain nitrogen equilibrium, or may do so only after prolonged periods of therapy. This also suggests that, even with good medical management and improvement, there is a narrow margin of nutritional safety and the cirrhotic has little to fall back on because of the chronic protein depletion.

Acknowledgment. Appreciation is expressed to the Laboratory of Brooke Army Hospital and to the Fourth Army Area Laboratory, Fort Sam Houston, Texas, for their numerous laboratory procedures, and to the dietitians of Brooke Army Hospital for their careful measurement of diets.

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BODY WEIGHT VERSUS WEIGHT STANDARDS IN CORONARY ARTERY DISEASE AND A HEALTHY GROUP *

By STANLEY M. GARN, *Boston*, MENARD M. GERTLER, *New York, N. Y.*,
SAMUEL A. LEVINE, F.A.C.P., and PAUL D. WHITE, F.A.C.P.,
Boston, Massachusetts

A NUMBER of authors have concluded that "overweight," as variously defined, was common among patients who died at a relatively early age of cardiac disorders.^{1,2} In general, their conclusions have been drawn from studies where the weight of the patients was compared to insurance company standards³ or to inductee standards.⁴ However, more recent studies have not verified the belief that weight elevated over optimal weight is by itself morbidogenic. Levy et al. concluded that "overweight alone did not increase to a significant degree the death rate with cardiovascular renal diseases."⁵

In reviewing many of these studies, it was noticed that the standards of comparison used were rarely fully applicable to the patients examined. Some of the norms in use today are from 15 to 40 years old and date back to times when the population was lighter in weight.⁶ In other cases, inductee or civilian norms were used to appraise the weight of veteran troops.⁴ Therefore, in the course of research on males who had experienced myocardial infarction prior to the age of 40, it was decided to compare these patients with normal, active, healthy men of comparable age, occupation and socio-economic status, since it was felt that such a group would be more nearly comparable to the patients than established norms, however well accepted. This report, then, presents data on the body weight in men who have experienced myocardial infarction prior to the age of 40, in comparison with the body weight of a comparable group of healthy males; both are given in comparison with a set of standard weights corrected for age and height.

MATERIALS AND METHOD

The two groups compared included 97 men who had experienced a myocardial infarction prior to the age of 40 and who were again active, and 146 healthy employed men who were of similar age, ethnic origin and occupation. During the examination, the maximum stature was taken, without shoes, to the nearest millimeter, and the weight was recorded to the nearest pound. Each individual was questioned as to his usual weight (the usual weight being that weight prior to the infarction in the case of the "coronary"

* Received for publication January 18, 1950.

From the Coronary Research Project, Cardiac Department, Massachusetts General Hospital and Harvard Medical School. Drs. P. D. White, H. B. Sprague, E. F. Bland, J. Lerman, S. A. Levine, and E. A. Hooton, Directors. Supported by a grant from the Commonwealth Fund, New York City.

group). Thus, the basic data included stature, weight and usual weight for the two groups.

The mean weight for the coronary group was 170.5 ± 2.31 pounds, and the comparable mean weight for the control group was 176.9 ± 2.01 pounds. Since the two groups differed in stature somewhat (171 cm. for the coronary group, in contrast to 176 cm. for the controls), the healthy group being the taller, it was necessary to make corrections for height in comparing weights. This was done by following the method of Levy et al. and calculating for each individual the deviation from the standard weight, according to height and age given in the Army 40-105 standards.⁵ The deviations from the standard were then summed up for both groups, as shown in table 1.

TABLE I
Deviations from "Optimal" Weight
(Calculated from Army 40-105 Age-Height Tables)

Deviation in Pounds	Control Group* (146)	Myocardial Infarction† Group (97)
100 to 109	1	0
90 to 99	0	0
80 to 89	2	1
70 to 79	0	0
60 to 69	2	2
50 to 59	6	2
40 to 49	9	9
30 to 39	20	11
20 to 29	21	20
10 to 19	41	20
0 to 9	16	12
-1 to -9	15	10
-10 to -19	8	8
-20 to -29	3	1
-30 to -39	2	1
Mean deviation in pounds	$+19.13 \pm 1.86$	$+18.49 \pm 2.14$

* Control group: mean stature $176.3 \pm .7$ cm., mean weight 176.9 ± 2.0 lbs.

† Myocardial infarction group: mean stature $171.8 \pm .6$ cm., mean weight 170.5 ± 2.3 lbs.

RESULTS

As shown in figure 1 a and b the average individual in each age group in both the comparison and the control groups was above the calculated norm-weight for age and height, with individual excesses as high as + 103 pounds. While the healthy, active males showed age-group deviations from + 4 to + 22 pounds above the norms, the men who had experienced myocardial infarction showed age group deviations of from - .8 to + 28 pounds. Both groups were statistically "overweight" as compared to the standards.

However, when the two groups were compared to each other in terms of the deviations from the norms, no real difference was seen. The age-group deviations showed the same pattern in both groups; the deviations from the normal standards were greatest at the younger age levels.

As shown in the figures, the root mean square deviations (figure 1 c) and the average deviations (figure 1 d) showed a close parallelism for both

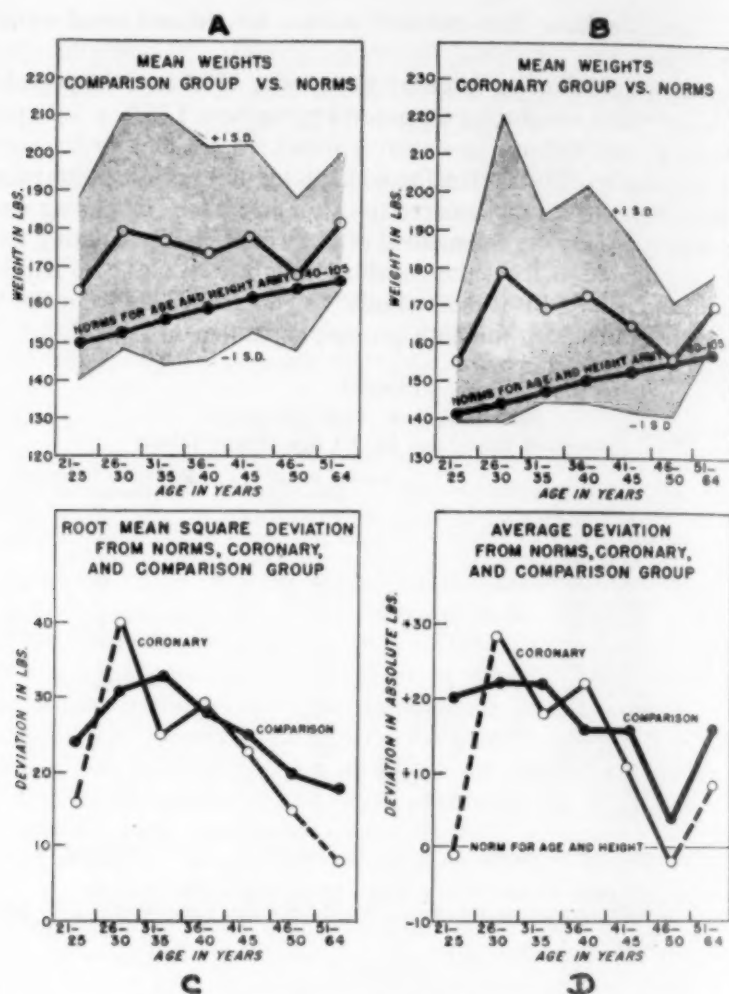


FIG. 1. Comparison of weights and corrected weights in the control group and the coronary disease group.

groups: both were "overweight" and to approximately the same degree. There was an average deviation of +18.5 pounds and +19.1 pounds for the group with myocardial infarction and the healthy control groups, respectively; accordingly, from the standards, both groups were "overweight."

DISCUSSION

From the foregoing data, it is seen that both the healthy normal males and those who had experienced myocardial infarction prior to the age of 40 showed statistical "overweight" in relation to the age-height-weight standards employed, and that the amount of "overweight" was statistically simi-

lar for the two groups. If the norms had been employed alone, without the control group, it would have been logical to call the young males with coronary heart disease "obese," and overweight would have been considered a possible etiologic factor in the development of the disease. But, since the healthy group in this study was equally "overweight," it was no longer possible to conclude that "overweight" was a predisposing factor. (There is, however, a difference in physique between the two groups; the relationship of physique to myocardial infarction is treated in a separate publication.⁷)

The same general findings have been noted by Moritz and Zamcheck⁸ and Yater and his associates.⁹ In the latter two studies, it was found that soldiers who died of coronary arteriosclerosis were "overweight" in comparison to inductees, but were not "overweight" in comparison to comparable soldiers who died as a result of accident.

It must be concluded, therefore, that men who experience myocardial infarction at a relatively early age are not, as a group, "overweight" or "obese," and that more care should be taken in employing "norms."

SUMMARY

1. We have compared, as to weight, 97 men who had experienced myocardial infarction prior to the age of 40 with 146 healthy men of comparable mean age, occupation and mode of living.

2. The actual weight of each individual was compared with the norm-weight calculated from Army 40-105 tables for age, height and weight.

3. Both groups were "overweight," in comparison with the norms at all age levels, and to the same degree, the average deviation being +18.49 and +19.13 pounds for the coronary heart disease group and the control group, respectively.

4. The present study serves to re-affirm the recent evidence that, when truly comparable control is used, those who experience myocardial infarction in early life are not more "overweight" or "obese" as a group than are the controls.

5. This study also serves to indicate the caution that must be exercised when employing norms, and it again questions the definition and meaning of "overweight." Perhaps both controls and coronary cases were actually overweight.

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SERUM URIC ACID IN RELATION TO AGE AND PHYSIQUE IN HEALTH AND IN CORONARY HEART DISEASE *

By MENARD M. GERTLER, *New York, N. Y.*, STANLEY M. GARN, and
SAMUEL A. LEVINE, F.A.C.P., *Boston, Massachusetts*

THE disease most frequently associated with an abnormal uric acid metabolism is gout.^{1,2} This association is based upon deposits of uric acid in the joints and connective tissue of gouty patients, usually in the presence of hyperuricemia.³ While the etiologic factors are unknown, it is generally agreed that the hyperuricemia is caused by endogenous factors in lieu of exogenous or renal factors. Additional observations which complicate the picture are: (a) the gouty diathesis may be present with⁴ or without⁵ an increase in the level of serum uric acid; (b) hyperuricemia occurs in families where gout has not been recognized.⁶

It has long been recognized that gout usually occurs in males of massive physique in the fifth or sixth decade, and is found infrequently in women, lean males or young males.^{1,7} Furthermore, one of the most commonly observed complications of gout is atherosclerosis.^{1,8} Whether the latter is a natural concomitant of the other factors, such as maleness, "massive physique" and age, or whether it is due to the deleterious effects of increased uric acid is unknown. It was of interest, therefore, to determine the level of uric acid in the serum in patients who have experienced myocardial infarction, since it has been shown that coronary heart disease under the age of 40 occurs usually in "males of massive physique."⁹ Furthermore, it was of interest to determine the associations or correlations of uric acid, not only in coronary heart disease but also with age and physique within a group of males who were free from any disease detectable by ordinary clinical evaluation.

The present report therefore concerns itself with the correlations and associations between serum uric acid and the variables: (1) age, (2) physique, (3) presence of coronary heart disease, and (4) absence of coronary heart disease.

METHODS AND MATERIALS

Serum uric acid was determined by the Folin method¹⁰ in each member of three groups of males. The first group consisted of 97 males who had experienced myocardial infarction prior to the age of 40. Ninety-two

* Received for publication February 1, 1950.

From the Coronary Research Project, Massachusetts General Hospital and Harvard Medical School, Drs. P. D. White, H. B. Sprague, E. F. Bland, J. Lerman, S. A. Levine and E. A. Hooton, Directors. Supported by a grant from the Commonwealth Fund, New York City.

determinations are reported in this group; five are not reported because of laboratory and technical difficulties. The second group included 146 men of comparable age who were free from illness as determined by history, physical examination and electrocardiogram. These men were active and working at the time this study was undertaken. The third group consisted of 97 males who were individually matched to the coronary disease group in age, physique, occupation, racial origin and economic status. Only 96 determinations are reported in this group, one determination being discarded because of technical difficulty. The last group was assembled to determine to what extent the "matched variables" would alter the serum uric acid level. The three groups described above will be known hereafter as (a) the coronary disease group, (b) the control group, and (c) the matched control group.

The relationship between serum uric acid and the variables of physique and age was computed by the use of the coefficient of correlation (designated as "r").¹¹ This coefficient measures the co-variance of two variables. This measure varies from 0, which means that there is no correlation, to +1 (perfect positive correlation) or -1 (perfect negative correlation). Other pertinent statistical methods are described in the text when employed. Physique was rated according to the somatotype method of Sheldon, thus giving three variables or components of physique to be considered separately.¹² These components are called ENDOMORPHY (softness and roundness), MESOMORPHY (bone and muscle), and ECTOMORPHY (linearity). Each of these three components is given a numerical rating (1 through 7), so that the values may be employed in the correlation coefficients. A complete somatotype profile would consist of ratings in these three variables. Thus, 3-7-1 would be an individual who possesses three points of endomorphy, seven points (maximal) of mesomorphy, and one point (minimal) of ectomorphy. He would be considered to be a dominant mesomorph with secondary dominance of endomorphy. Also, for simplification of presentation, a fourfold classification of physique was used.

1. ENDOMORPHS: those showing relative preponderance of endomorphy.
2. MESOMORPHS: those showing relative preponderance of mesomorphy.
3. ECTOMORPHS: those showing relative preponderance of ectomorphy.
4. MID-RANGE: those showing about equal proportions of the three components.

In connection with this work on coronary heart disease, a new index or ratio, cholesterol/lipid-phosphorus x uric acid, is introduced as having possible selective and predictive value.

RESULTS

1. *Age and Serum Uric Acid.* The possibility of a rise in serum uric acid associated with age was investigated by computing the uric acid means

for the third, fourth and fifth decades in the control group and in the coronary disease group. The results are summarized in table 1.

From the data in table 1, there is no evidence of an age-associated rise in serum uric acid in either group between the third and fifth decades; the content of uric acid in the serum of the coronary disease group averaged .6 mg. per cent more than in the control group. Furthermore, the lack of age-correlated rise in uric acid was confirmed by the coefficients of correlation,

TABLE I
Serum Uric Acid by Decades
Control Group and Coronary Disease Group

Decade	Control Group		Coronary Disease Group	
	No.	Uric Acid	No.	Uric Acid*
20-29	21	4.63±.16	7	5.27±.41
30-39	73	4.73±.09	50	5.12±.16
40-49	46	4.53±.09	35	5.11±.18
Total	140†		92	

* All uric acid values given in this paper are in milligrams per cent. The figures refer to the mean ± the standard error of the mean unless otherwise noted. (See Mainland, 1939.¹³)

† Six individuals over 50 are not included.

which were $+.01 \pm .10$ and $-.09 \pm .08$ for the coronary disease group and the control group, respectively. From the facts presented, it is reasonable to conclude that serum uric acid does not rise with age during the third, fourth and fifth decades.

2. *Physique and Uric Acid.* In order to assess more definitely the clinical observation that "massiveness" of physique is associated with gout

TABLE II
Coefficients of Correlation (*r*) between Serum Uric Acid and Other Variables
in the Control Group and in the Coronary Disease Group

Correlation	Control Group	Coronary Disease Group
Stature	-.07±.08	+.10±.10
Weight	+.30±.08*	+.23±.10*
Ponderal Index	-.37±.07*	-.22±.10*
Endomorphy	+.30±.08*	+.29±.10*
Mesomorphy	+.23±.08*	-.05±.10
Ectomorphy	-.29±.08*	-.13±.10

* Significant.

and therefore hyperuricemia, coefficients of correlation were calculated between serum uric acid and the following variables: stature, weight, ponderal index (height over the cube root of weight), endomorphy, mesomorphy and ectomorphy. The results of these calculations are recorded in table 2.

It may be ascertained from table 2 that serum uric acid rises with both weight and body mass * in both the control group and the coronary disease

* The ponderal or height/3√weight index is a measure of body build; ratios approaching 10.0 indicate laterality of build, while ratios approaching 14.0 indicate linearity of build.

group. Similar trends are observed with the physique components in the normal group. The same general trend is observed in the coronary disease group, but attention should be called to the marked decline in the correlation value in the coronary mesomorphs in contrast to the control mesomorphs. Thus, in both groups the serum uric acid increases as the physique becomes more massive, especially when the physique is due to softness and roundness (endomorphs). On this basis it is to be expected that the massive physiques (endomorphs and mesomorphs) will have a higher level of uric acid in the

TABLE III
Serum Uric Acid in Various Physiques

	Control Group		Coronary Disease Group	
	N	Uric Acid	N	Uric Acid
Endomorphs	51	4.87 \pm .12	23	5.61 \pm .23
Mesomorphs	34	4.59 \pm .09	41	4.98 \pm .18
Ectomorphs	34	4.34 \pm .13	9	4.80 \pm .23
Mid-range	27	4.65 \pm .12	19	5.01 \pm .27

serum than will the linear or ectomorphic physiques. This trend is shown in table 3.

As shown in table 3, by using the physique groupings described earlier, the soft, large endomorphs have the highest serum uric acid in both groups, while, in contrast, the linear ectomorphs have the lowest serum uric acid in both groups. Though it was expected that the muscle mass of the mesomorphs would contribute to their serum uric acid, the dominant mesomorphs did not differ appreciably from the mid-range physiques, thus con-

TABLE IV
Difference in Serum Uric Acid between the Mid-Range Physique
and the Other Physiques

Difference in Serum Uric Acid between Mid-range Physique and	Control Group	Coronary Disease Group
Endomorphs	+ .22	+ .60
Mesomorphs	- .06	- .03
Ectomorphs	- .31	- .22

firmed the lack of correlation between mesomorphy and uric acid in the coronary disease group.

The differences between the mid-range physiques and the other three physiques in the control group and the coronary disease group are listed in table 4 (see figure 1).

The data from tables 3 and 4 reveal that the large soft endomorphs, rather than the men with predominantly muscular physiques, have the highest serum uric acid level. Furthermore, in the presence of coronary heart disease this condition is exaggerated and the serum uric acid in the coronary

endomorph exceeds expectation significantly. Thus the abnormality of the uric acid metabolism in the presence of coronary heart disease differs from the abnormality of cholesterol metabolism, where it has been shown that in the presence of coronary heart disease it is the mesomorph who displays the exaggerated cholesterol change.¹⁰

3. *Serum Uric Acid in Health and in Coronary Heart Disease.* Tables 2, 3 and 4 reveal that the level of uric acid in the serum was higher in the

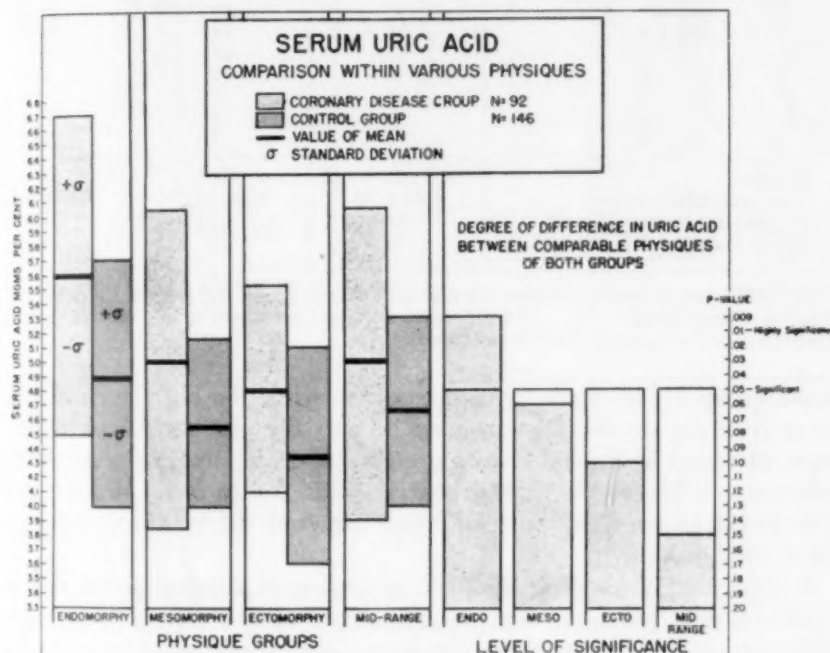


FIG. 1. Serum uric acid values of the various physiques within the coronary disease group and the control group.

coronary disease group than in the control group when the comparisons were made on the basis of age or physique. This difference is more apparent when the two arrays are contrasted in table 5 below.

It is noted from table 5 that (a) the mean value of serum uric acid in the coronary disease group is higher than the control group and the matched control group, and (b) the entire frequency distribution is raised. Far more individuals in the coronary disease group come within the realm of hyperuricemia (variously defined as above 5.0 or 6.0 mg. per cent). While only 6 per cent of the control group and of the matched control group possess serum uric acid levels above 6.0 mg. per cent, 24 per cent of the coronary disease group possess similar levels.

The matched control group possesses, on the average, a higher level of serum uric acid than the control group but a lower level than the coronary

TABLE V
Serum Uric Acid in the Control Group, the Coronary Disease Group
and the Matched Control Group

Mg. Per Cent Serum Uric Acid	Control Group	Coronary Disease Group	Matched Control Group
2.5-2.9	1	0	0
3.0-3.4	4	5	2
3.5-3.9	20	9	8
4.0-4.4	38	15	24
4.5-4.9	38	19	23
5.0-5.4	23	14	20
5.5-5.9	13	10	13
6.0-6.4	7	6	4
6.5-6.9	2	6	2
7.0-7.4	0	5	0
7.5-7.9	0	3	0
Number	146	92	96
Mean \pm standard error	4.64 \pm .06	5.13 \pm .12*	4.85 \pm .07
Per cent above 5 mg. per cent	31	48	42
Per cent above 6 mg. per cent	6	24	6

* The differences of means between the coronary disease group and both of the other groups are highly significant ($p = .01$). The difference between the means of the control group and the matched control group is significant ($p = .05$).

disease group. This strongly suggests that, while the high levels of serum uric acid in the coronary group may be partially attributed to a physique factor, there are additional factors present. For, if physique were the only factor responsible for the high uric acid within the coronary disease group, there would be no significant difference between the levels of serum uric acid in both groups.

4. *Diet and Serum Uric Acid.* The finding of a higher serum uric acid in endomorphic physiques and in individuals with coronary heart disease raised the possibility that these significant differences could be due to differences in ingestion of purine-containing foods. This possibility was investigated by calculating the purine intake from dietary studies of the individuals concerned. It was found that the purine intake of the control group was $1.49 \pm .06$ gm. per week, as compared to $1.15 \pm .05$ gm. per week in the coronary disease group. Accordingly, the higher serum uric acid in the coronary disease group could not be attributed to a greater ingestion of purines. Further calculations revealed (a) no correlation between the amount of purines ingested and the level of uric acid in the serum for either group, and (b) no physique differences in the amount of purines ingested.

Thus it is apparent that dietary factors do not contribute significantly to the level of serum uric acid in either the control group or the coronary disease group.

5. *The Uric Acid Screening Ratio.* In previous publications it has been shown that the ratio of cholesterol/lipid phosphorus (or lecithin) was more

TABLE VI
Uric Acid Ratio $\frac{\text{Cholesterol}}{\text{Lipid Phosphorus}} \times \text{Uric Acid in the Control Group,}$
Matched Control Group and the Coronary Disease Group

Ratio Value	Control Group	Coronary Disease Group	Matched Control Group
40-59	5	1	2
60-79	51	2	22
80-99	53	11	32
100-119	29	19	19
120-139	6	13	7
140-159	2	7	1
160-179	0	5	0
180-199	0	1	0
Number	146	59	83
Mean \pm standard error	87 \pm 2	119 \pm 4	92 \pm 2
Per cent below 119	94.5*	50.0*	90.4*
Per cent above 119 +	1.13	18.0	1.5
Per cent below 119 - σ = 91	61.0	18.6	55.0

* Fifty per cent are always below the mean.
 σ = standard deviation.

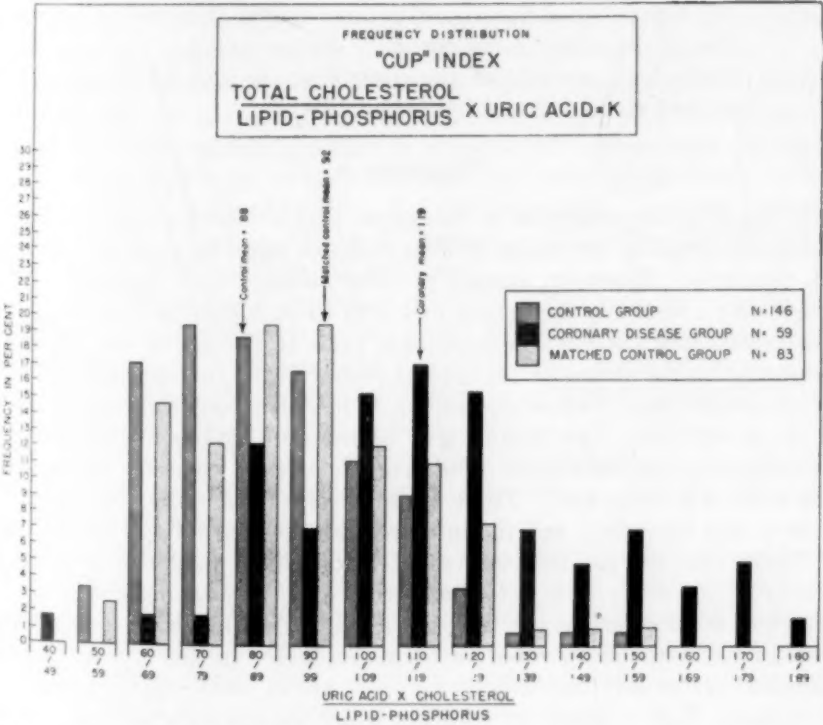


FIG. 2. Values of "cup" or uric acid index in the coronary disease group, the control group and the matched control group.

effective in separating coronary-prone individuals from a healthy population, than the absolute value of either constituent alone. The form of the ratio, cholesterol/lipid phosphorus (or lecithin), was dictated by the observations^{14, 15, 16} that cholesterol was more causally related to atherosclerosis, while lecithin was more protective against atherosclerosis. Since it has been shown that high uric acid levels also may be associated with atherosclerosis, it was decided to incorporate it into the ratio in the hope of obtaining a ratio which would show a greater dichotomy for the precoronary healthy state and the noncoronary healthy state. The ratio was then adopted as:

$$k = \frac{\text{cholesterol (mg. per cent)} \times \text{uric acid (mg. per cent)}}{\text{lipid phosphorus (mg. per cent)}}$$

As shown in table 6, this ratio is effective in producing a more marked separation between the coronary disease group and the two healthy groups than was possible heretofore. The mean value of the ratio for the two healthy groups approximated 90, while the mean value of the ratio in the coronary disease group approximated 119. The effectiveness of the ratio may be gained from the following observations (see figure 2).

- (a) Only 6 per cent of the control group equaled or exceeded 119 (mean value of the index in the coronary disease group).
- (b) Ninety-four per cent of the control group and 90 per cent of the matched control group fell below 119.

DISCUSSION

It has been demonstrated in this paper that the serum uric acid level in man is significantly altered by neither diet nor age (between the third and fifth decades). However, certain positive findings were apparent. These include (a) a tendency for serum uric acid to be higher in individuals who have experienced coronary heart disease prior to the age of forty, and (b) a tendency for the serum uric acid to be higher in the endomorphic physiques in both control and coronary groups. It has also been shown that a ratio which incorporates cholesterol, lipid phosphorus and uric acid more effectively separates individuals who have experienced coronary heart disease from those who have not. These findings raise questions as to the validity of the study, its utility, and the interpretation of the findings themselves.

There are two possible sources of error which may detract from the validity of the study: the individual error and the systematic error. The individual error refers to the fact that a single determination may be either above or below the mean value for the individual. In this type of study the individual errors are randomized, for there are as many readings which are apt to be too high as there are readings which are apt to be too low. Therefore, the mean values of the determinations would be repeatable to within the \pm error values. Hence, the mean values may be considered correct to

within \pm standard error. The systematic error refers to regular errors in the technic of determining the content of uric acid in the serum. Such errors include (a) imperfect separation of sodium urate during the protein separation phase, and (b) chromogenic reaction between sodium urate and phosphotungstic acid, which is not specific, for it is also given by such substances as phenols, hemoglobin and chlorophyll.¹⁴ Since the systematic errors are constant, and all determinations were made by the same laboratory, the net effect would cancel out in comparing the three groups considered here.

The range and means of the values obtained in the control group and the matched control group are noteworthy. The values of the means approximate other published values from this hospital.² However, a large proportion of individuals exceed the commonly quoted "upper limit of normal." If 5.0 mg. per cent is considered as the "upper limit of normal," it is found that more than 30.0 per cent of either control group exceeds this value. If 6.0 mg. per cent is accepted as the upper limit of normal, then 6.0 per cent of either control group exceeds this value. It is noteworthy at this juncture to mention that not only is the mean value of serum uric acid significantly higher in the coronary disease group, but 24 per cent of the individuals within the coronary disease group possess serum uric acid values greater than 6.0 mg. per cent. These findings lead to two possible conclusions: (a) that the accepted "range of normal" must be revised upwards, or (b) that hyperuricemia exists without the signs or symptoms of gout.

The first conclusion appears reasonable when the physique correlations are considered. It is evident that the expected serum uric acid is 0.5 mg. per cent higher in endomorphs than in ectomorphs. Since such differences exist, it is reasonable to contend that each physique group should have a different range of normal values. By such standards, a serum uric acid value of 6.0 mg. per cent would be of greater significance in an ectomorphic individual than in an endomorphic individual.

When the marked and important uric acid differences between the control groups and the coronary disease group were first evaluated during the course of this study, it was thought that they could be due either to a predominance of certain physiques in the series or to a partial correlation with serum cholesterol. Both of these possibilities proved untenable when investigated. The differences remained when the corrections for physique were made, and the correlation coefficient between uric acid and cholesterol was insignificant, being $+ .01 \pm .10$.

What explanation may be given for the coexistence of a higher serum uric acid and a higher serum cholesterol in coronary heart disease? Although hyperuricemia⁶ and hypercholesteremia¹⁸ are inherited as simple Mendelian dominants, there is no available evidence which proves genetic linkage or polytypic expression. Until a suitable explanation is offered for the association of hyperuricemia and hypercholesteremia in coronary heart disease, it is reasonable to contend that the association is random or accidental, but its importance should not be minimized. It suggests that in-

dividuals who possess both hyperuricemia and hypercholesteremia are more likely to develop coronary heart disease than those individuals who do not possess these conditions. This concept is more tenable if one considers the "uric acid ratio."

Furthermore, the concept of hyperuricemia and hypercholesteremia as two important factors in the precoronary state is strengthened by the association of those variables in the physiques most prone to coronary heart disease. The dominant mesomorphs with coronary heart disease possess serum hypercholesteremia +++ and hyperuricemia ++, while the dominant endomorphs with coronary heart disease possess serum hypercholesteremia ++ and hyperuricemia +++.¹⁰

At present there is no satisfactory explanation as to how cholesterol and uric acid interrelate in coronary heart disease. It is possible that uric acid in its lactam state may be a powerful cationic surface agent, and perhaps attach itself to the larger cholesterol molecule and bring the cholesterol molecule into contact with a surface such as arterial intima.

SUMMARY

1. Serum uric acid determinations were made on three groups of individuals. These groups were (a) 146 healthy working men, (b) 92 men who had experienced myocardial infarction prior to the age of 40, and (c) 97 healthy men who were "matched" to the men of the coronary disease group.

2. The levels of the serum uric acid were $4.64 \pm .76$, $4.85 \pm .74$ and 5.13 ± 1.10 for the control group, matched control group, and the coronary disease group, respectively.

3. Twenty-four per cent in the coronary disease group and 6 per cent in both the control group and the matched control group possess levels of serum uric acid of 6 mg. per cent or over.

4. There is no age rise in serum uric acid from the third to the fifth decades in either the coronary disease group or the control group.

5. A physique difference of serum uric acid levels is apparent. The dominant endomorphs in both the control group and coronary disease group exceed all other physiques in the content of uric acid in the serum; the dominant ectomorphs have the smallest amount of uric acid in the serum.

6. In coronary artery disease, the uric acid physique difference is accentuated. The rise in serum uric acid in the presence of coronary heart disease is 15.19 per cent in the endomorphs, 8.49 per cent in the mesomorphs, and 3.22 per cent in the ectomorphs.

7. There is no relationship between the ingested purines and the level of serum uric acid.

8. The ratio, uric acid times cholesterol/phospholipids, is considered to be of more value in assessing the biochemical background of the coronary disease state than is either of the constituents considered separately.

Acknowledgment. The authors wish to express their thanks to and acknowledge the statistical assistance of Mrs. Jennifer Lehmann and Mrs. Neria Ryder.

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TREATMENT OF AMEBIASIS WITH ATABRINE COMBINED WITH CARBARSONE *

By RYLE A. RADKE, Lieutenant Colonel, M. C., U. S. Army, F.A.C.P.,
Fort Knox, Kentucky

IN 1946, at Letterman General Hospital, a patient with amebiasis in whom a liver abscess had penetrated the diaphragm, and in whom a bronchopleural fistula was present, had remained critically ill and continued to produce copious brown sputum in spite of having received two courses of 10 gr. of emetine in less than a month. Lt. Col. Vince Moseley and I decided to treat him with atabrine because we reasoned that, since Galli-Valerio¹ had shown that atabrine was effective in treatment of *Giardia lamblia* infections, and since the *Giardia* was known to inhabit the biliary system, atabrine must be present in the bile in effective quantities. We further reasoned that the position of the malarial parasite and the flagellates in the animal kingdom was not far removed from that occupied by the amebae. The clinical response was amazing. In four days the patient's temperature was normal and sputum production soon ceased. Realizing that the results in one case which had been treated with other drugs could have been fortuitous, I set out to determine, if possible, the amebicidal effects of atabrine.

It is not within the scope of the present paper to review the therapy of amebiasis. The interested reader is referred to Hargreaves'² excellent review, or to Craig's³ work. It appears obvious to me that, when the therapeutic effort of choice is a drug whose toxicity is as great as that of emetine and whose therapeutic effectiveness is as debatable, the time has come to make a determined effort to find one more effective and less toxic. Klatskin and Friedman⁴ have recently reported that complications followed treatment in 91 per cent of a group of patients treated by them with emetine. My personal experience with the drug makes it possible for me to accept their data without reservation. Little mention is made of the severe fatigability frequently encountered in patients who have received emetine. At Madigan General Hospital, where daily electrocardiograms were taken during the course of emetine therapy, eight of 10 consecutive cases had significant changes in the tracings, usually in the T waves. Merritt⁵ has reported changes in the electrocardiograms in 74 per cent of 38 cases treated with emetine. That no drug has yet been found which is effective by itself in treatment of amebiasis is apparent from the fact that two or more drugs are combined in each recommended therapeutic régime from the British² and United States Army⁶ official publications. With such combinations, the success rate has varied between 50 and 75 per cent. With the addition of

* Read before Regional Meeting, American College of Physicians, Louisville, Ky., December 10, 1949. Received for publication March 10, 1950.

From Medical Service, Station Hospital, Fort Knox, Kentucky.

penicillin and sulfadiazine to emetine, chiniofon and carbarsone, as recommended by Hargreaves, Nix⁷ was able to report a success rate of 85 per cent. In reviewing the literature with specific reference to treatment of amebiasis with atabrine, I found that Bernstein⁸ reported in 1946 on the treatment of 30 cases of amebiasis with atabrine in two courses of 0.1 gm. thrice daily for five days, separated by a few days of rest. His employment of the drug resulted from his observing its apparent effect on amebiasis when given for treatment of a case of amebiasis complicated by *Giardia lamblia*. Jones⁹ in 1946 reported evidence, from experimental infections in rats induced by intracecal injections of *Endameba histolytica* and mucin, that atabrine was of the same order of effectiveness as emetine in treatment of his experimental infections. I found mention in the literature of two cases of amebiasis treated with atabrine for associated *Giardia lamblia* infections in which temporary improvement was said to have occurred.^{10, 11} A third case, reported by Spellberg and Zivin,¹² was one of amebic abscess of the liver; when antimalarial treatment with atabrine was carried out, temporary improvement of the patient's condition was reported. A second case of amebic liver abscess treated with atabrine for malaria, reported in the same paper, was not accompanied by a reported improvement. Hargreaves,² in his review of the treatment of amebiasis in 1946, mentioned without elaboration that, among a number of other drugs, mepacrine (atabrine) had been used in the treatment of amebiasis.

Jacobs et al.¹³ report that the incidence of *E. histolytica* as revealed by stool examinations of soldiers was 10.1 per cent in 1,317 men who served in the United States only; 18.5 per cent in 1,347 men who served in European Theatre of Operations, including Africa and the Middle East, and 13.7 per cent in 952 men who served in the Pacific theatre. The difference observed between men from the Pacific and the European Theatres is significant, having an epsilon of 121.5 where any value above three epsilon is significant. Having served in the two theatres during the war, I felt that the most significant difference between the two areas was the widespread employment of atabrine as a malarial suppressive agent in the Pacific Theatre, contrasted with reliance, primarily, upon environmental control measures in the ETO. I am certain that other differences between the areas will be immediately apparent: first, more vegetables were available in the ETO, most of them grown with "night soil" for fertilizer; and second, and equally important, the peoples of Europe appeared somewhat less exotic than the South Pacific peoples, and water from other than engineer-treated water points was more acceptable to the soldier without the precaution of adding halazone tablets (Stone¹⁴ having shown the cysts of *E. histolytica* to be susceptible to such concentrations of chlorine). However, the fact that this difference has occurred is suggestive of atabrine effect on the *E. histolytica*.

The first thing done in the present study was to assess the in vitro effect of atabrine upon the *E. histolytica*. This was done by means of egg slant cultures and liver infusion cultures of the amebae, to which known quantities

of atabrine were added to the serum and Locke's solution mixture which overlies the egg slant or liver slant. Klein and Radke¹⁸ found that atabrine consistently had the effect of causing definite and fairly rapid diminution of the growth curve of the ameba (number of organisms plotted against time), and of causing rapid disappearance or encystment of the remaining

TABLE I
Technic of Experiment

- a. 1 c.c. of drug in Locke's solution added to vigorous 24 hour culture.
 b. Smears made from 0.1 c.c. of material from junction of serum and rice powder.
 c. Negative smears and smears with cysts alone subcultured.
 d. Results recorded as follows:
- 4+ 10 or more amebae per L. P. F.
 3+ 5 to 10 amebae per L. P. F.
 2+ 2 to 5 amebae per L. P. F.
 1+ Less than 2 amebae per L. P. F.

organisms. In comparative tests using atabrine, carbarsone, emetine and diodoquin, we found that atabrine's effect was of the same order in vitro as that of emetine, and that both atabrine and emetine were inferior to carbarsone in causing the amebae to disappear under the conditions of our experiment. Data from typical experiments are shown in tables 1, 2 and 3. Because of the variables injected into the experiment by the bacteria present,

TABLE II

	Hours			
	24	48	72	96
Emetine (1-3000)	4+	4+	neg.	neg.
Emetine-diodoquin (1-3000-1-1500)	2+	2+	neg.	neg.
Emetine-atabrine (1-3000-1-3000)	1+	1+	neg.#	neg.
Carbarsone (1-1500)	1+	neg.	neg.	neg.
Atabrine (1-10,000)	1+	1+	1+	neg.#
Control	2+	4+	4+	4+
Control	2+	4+	4+	3+

Subculture positive.

and the possible effect of absorption of the drug on the solid media, as shown by Laidlaw, Dobell and Bishop,¹⁶ an attempt was made to find a more effective culture medium. We became aware of the work of Shaffer and Frye^{17, 18, 19} on the culture of *E. histolytica* in a relatively bacteria-free medium. Part of this ameba culture technic consists in the use of a liquid thioglycolate medium which is conditioned to satisfy the growth needs of

amebae by the inoculation of a strain of streptobacillus. This organism is partially removed from the medium prior to its use in ameba culture by centrifugalization, and its further growth is inhibited by the addition of penicillin. We isolated a streptobacillus organism from one of our *E. histolytica* cultures that had been obtained from the Army Research and Graduate School and that appeared capable of sustaining the growth of the *E. histolytica* under the conditions Shaffer and Frye have described. However, in our hands the growth curves of *E. histolytica* in this medium could not be stabilized sufficiently to permit us to evaluate the drug effect. We did find that the addition of atabrine apparently affected neither the growth of the streptobacillus which we isolated nor the subculture of streptobacillus which we obtained through the courtesy of Dr. Shaffer.

TABLE III

	Hours						
	24	48	72	96	120	144	192
1. Atabrine (1-3000)	1+	2+	c	c	c	c	neg.
2. Atabrine (1-6,000)	1+	1+	c	neg.	neg.	c	neg.
3. Atabrine (1-30,000)	3+	1+	c	1+	neg.	neg.	neg.
4. Atabrine (1-60,000)	2+	1+	2+	1+	c	2+	c
5. Control	2+	1+	4+	3+	2+	2+	neg.
6. Control	1+	2+	4+	2+	2+	2+	1+
7. Control	2+	4+	3+	2+	1+	1+	1+

Subcultures from 1, 2 and 3 negative at 96 hours and beyond, all subcultures negative at 192 hours except controls 6 and 7.

The in vitro data presented above serve as presumptive evidence of atabrine effect upon the *E. histolytica* organism. First, the fact that the *E. histolytica* will grow well upon the medium described by Shaffer and Frye has been confirmed by us as well as by other observers. Second, we found no appreciable effect upon the growth curve of the streptobacillus when atabrine was added to the culture. From that, we have reasoned that there is no direct effect by atabrine upon the bacterial substrate of sufficient degree to account for the effect of atabrine on the ameba culture. Third, when added to the cultures of *E. histolytica*, atabrine has produced in each instance a marked amebacidal effect after having been in contact for a number of hours. We believe the presence of cultures containing viable cysts after rather prolonged exposure to atabrine indicates clearly the necessity of an additional therapeutic agent effective against the cystic form of *E. histolytica*.

We then turned to animals as hosts of experimentally induced amebiasis. We were reluctant to embark upon an attempt to evaluate the therapeutic effectiveness of atabrine in the management of lesions produced in the bowels of animals, where the tendency is to spontaneous recovery, so an attempt was made to produce cutaneous amebiasis in the kitten, cat and rabbit. About one-third of the injection sites developed granulomatous lesions. However, we felt that the cutaneous lesions which we produced were too inconstant and too likely to be confused with bacterial infection results, despite the fact that we had apparently cared for the bacterial substrate by treatment of the animal after inoculation with combined streptomycin and penicillin. Consequently, another approach to the problem was sought. The idea of using a method of assessing the results of therapy by direct visualization of the lesions in the rectosigmoidal area of the human intestine was conceived. Human bowel lesions have often been employed as a means of following response to therapy.^{20, 21, 22, 23, 24, 25, 26} I believe it furnishes a reliable index of response to therapy only when all the sigmoidoscopic examinations are done by the same observer, as was the case here.

Twenty-five cases of intestinal amebiasis, in which ulcerations were seen through the sigmoidoscope, have been treated with atabrine at Station Hospital, Fort Knox, Kentucky. These cases were consecutive, except for those with no lesions visible, three in whom follow-up observation was inadequate, and two in whom treatment was discontinued as discussed below. Eleven of these cases were observed for periods varying from 10 to 60 days before treatment was started, and in none did the lesions heal spontaneously. A group of four of the 25 cases was then treated with atabrine alone, in doses of 0.1 gm. three times a day for 10 days. Because of the finding of cysts of *E. histolytica* in the sigmoidoscopic specimen of one case after such therapy, even though the ulcers had healed, we extended the atabrine treatment period to 15 days and increased the daily doses to four. It was decided, as a result of the in vitro work and the above experience, that atabrine is apparently unable to destroy the encysted form on all occasions. Therefore, an additional agent, capable of destroying the cystic stage of the organism, would be required for successful therapy.

Carbarsone appeared to us the most effective agent in destroying the cysts in vitro, so we decided to employ it in the usual dosage of 0.25 gm. twice or thrice daily (depending on the patient's size) for a 10 day period in addition to atabrine.

Initially, the cases were treated with atabrine alone and then sigmoidoscoped prior to the employment of carbarsone. After 10 such cases had been treated a case was observed in which, although the ulcers were healed after the course of atabrine, they recurred to a slight degree while the patient was receiving carbarsone. Consequently, it was decided that the two drugs should be employed concurrently wherever possible.

The results of the use of atabrine alone, judged by means of sigmoidoscopic examination, were that there was healing of the rectal lesions in the

10 cases in which it was employed first, except for the presence of submucosal hemorrhage in one case. In the 15 cases in which the atabrine and carbarsone were given concurrently, the rectal lesions were healed in all instances except for the presence of submucosal pigment spots (vide infra), ulcers in one case from which the amebae could not be recovered, and a submucosal hemorrhage in one case. The cause of these hemorrhages is not clear. However, in both instances the blood was pipetted and examined, and no amebae were seen in it nor did any grow in the culture. All cases were sigmoidoscoped at the end of therapy and, where possible, every two or three months since then. Twenty-three of the cases have had two or more follow-up sigmoidoscopic examinations at these intervals. In one case the follow-up examination has been by sigmoidoscopic examination performed by another. (Table 4 shows the length of follow-up in days.)

Of the 25 cases, two were acute amebic dysentery in the sense of having severe bloody diarrhea, large, widespread rectosigmoidal ulcerations and marked systemic reaction. Both of these were treated with atabrine alone for 15 days, at the end of which time the bowel was completely healed except for the presence of the pigment spots and a submucosal hemorrhage in one.

TABLE IV		
Length of Sigmoidoscopic Follow-Up in Days		
60-90	90-150	150-240
2	5	8
240-300	300-395	
4	6	

The smears were negative in both; however, one relapsed during carbarsone therapy. Two of the cases were chronic amebic hepatitis, one of them having had earlier and unsuccessful treatment with emetine and diodoquin. The liver involvement as well as the bowel lesions responded to therapy, and both patients have remained apparently well for 12 months; the bowel is free from ulcers, while the liver involvement is quiescent if not healed. Twenty-one of the remaining cases had chronic symptoms, referable to the bowel, of diarrhea, lower abdominal cramping and precipitate stools. All but one of the 25 cases presently discussed had had symptoms of the disease for longer than 90 days, and six of them had been previously unsuccessfully treated with emetine and carbarsone or diodoquin.

An assessment of the treatment results is as follows: One case in which first atabrine and then carbarsone were used successively had cysts of *E. histolytica* at the completion of the atabrine phase of the treatment but had no amebae or cysts upon completion of the carbarsone phase, and has remained so for 12 months. This is not considered a failure because of our assumption that the addition of a drug capable of destroying the cysts would be necessary.

One case was ameba-negative and the ulcers were healed, with only pig-

ment spots remaining upon completion of the atabrine phase of the treatment, but there was recurrence of ulceration at the site of several of the submucosal pigment spots upon completion of the carbarsone phase.

One case had cysts in the fecal stream immediately upon completion of the combined atabrine-carbarsone therapy, but these have been absent from three examinations since then with no further treatment; however, this is considered a failure.

One out-patient, after combined therapy, had two large ulcers unhealed from which no organisms could be recovered. Since the patient was not discolored from the atabrine, he probably had not taken the prescribed dose. The ulcerations were healed and he was yellow upon completion of a course of therapy administered under supervision. Thus, if one takes the proved relapses from the viewpoint of demonstration of the organism, one has two cases, or 8 per cent, out of 25 cases treated by means of combined therapy. The same is true if one considers failure of the ulcers to heal during combined therapy. However, one case had ulcerative failure and organisms were recovered. Therefore, one finds that 12 per cent is the total relapse rate. To date the only observed treatment failures have been found immediately after termination of therapy, in other words, within 25 days of start of therapy.

In addition, I recorded subjective response to therapy. In all instances, subjective relief was great. In all but two instances there were appreciable gains in weight, ranging from five to 30 pounds. Several instances have been observed in which, after a shorter or longer time of relief of symptoms, a recurrence of symptoms has been noted of relatively acute onset and short duration. In each instance, sigmoidoscopic examination has been negative when done at these times.

Complications of therapy have been as follows: All cases treated with atabrine developed a deep yellow coloration, with the exception of the case in which the ulcerations did not heal, mentioned above, and that patient developed the coloration when given the medication under supervision. One case treated with combined therapy developed toxic delirium on the eleventh day which cleared up promptly when the atabrine was discontinued. Another man, while taking the combined treatment, developed an acute schizophrenic episode which two consultants in psychiatry believed was precipitated not by the drug but by the sigmoidoscopic examination. These latter two cases are not included in the 25 cases under discussion because treatment was not completed. Two cases on an out-patient status complained of vomiting while taking the drugs. This was not evident when treatment was continued in the hospital. There were two types of adverse reaction to carbarsone, namely, dermatitis and diarrhea. One case of arsenical dermatitis occurred in a man previously treated for syphilis with arsenic. This cleared up promptly upon termination of treatment and administration of BAL. Diarrhea of minor degree occurred frequently while carbarsone was being ad-

ministered. In no instance was this more than three stools per day. Thus, the only complications which have necessitated discontinuance of therapy have been toxic delirium and dermatitis. Therapy of the schizophrenic was discontinued because of his mental disease.

In my opinion, the value of the sigmoidoscopic examination in the diagnosis of amebiasis—when employed in conjunction with smears and cultures examined and inoculated at once in the examining room—has been underrated. The lesions of amebiasis are apt to be overlooked if the examination is not carefully done, and this may explain the differences recorded by Craig³ in support of his opinion that the routine employment of the sigmoidoscope in the diagnosis of amebiasis should be discouraged. In our hands, sigmoidoscopic examination has been the most reliable diagnostic method. The smears are examined at once in the examination room and cultures inoculated at once also. I believe that our success with this method is due partly to the fact that the search for the organism is more carefully done when it is made under the doctor's eye, and partly to the fact that when lesions are observed the specimen for examination is obtained by pipetting the contents of the lesion. For the above reason, we have made the criterion of cure in this group of cases the presence of negative smears and cultures obtained at sigmoidoscopic examination.

I believe, in preparation for sigmoidoscopic examination, the patient should be given a tap-water enema one-half hour after eating, followed in another half hour by the examination. This sequence is observed in order to take advantage of the gastrocolic reflex in securing evacuation of the enema. Soapsuds are irritating to the bowel mucosa and should not be employed in preparation for this examination because the resultant reddening and edema of the mucosa obscure the smaller lesions of amebiasis.

The sigmoidoscopic examination per se is not painful if carefully done, with attention to the lubrication of the anal canal and care that no hair is carried into the anal canal with the instrument. A further cause of pain is the stretching of the bowel by manipulation of the instrument. If this is avoided and the anal canal well lubricated, the examination, although uncomfortable, is not painful. A further cause of distress on the part of the patient is his fear that he will move his bowels, and he should be assured prior to the start of the examination that, though the instrument will stimulate his bowel to a vigorous call to stool when the rectosigmoidal junction is passed, he will not disgrace himself. In some hyperactive individuals, this stimulation is apparently interpreted as pain. I employ a suction machine with an open-end woven catheter to remove mucus and fecal particles from the field, and specimens are secured by bacteriologic pipette of 1 c.c. size with suction furnished by a rubber bulb from a medicine dropper.²⁷ The bowel lesions of this disease have been described by many observers.³ However, I believe that there is widespread misapprehension concerning the appearance of these lesions. Many observers describe as typical the small ulcer with

overhanging edges of ragged mucosa. My own opinion about the matter is that the typical lesion is small, varying in size from a pinpoint to one millimeter, and with a brownish-red elevated center. These are found typically in small aggregations of four to six or more, and when ulcerations are present these lesions in almost every instance may also be observed nearby. Upon pipetting the contents of these small abscesses, an ulceration 2 mm. or more in diameter is left in the bowel at the site; this represents the submucosal burrowing so characteristic of the *E. histolytica*. I have also observed and secured the organism from rather large superficial erosions, like those described by Faust²⁸ in his study of the New Orleans autopsy material; and in two cases which we were following prior to starting treatment we found minute abscesses, such as were described above, to have appeared within the confines of such superficial erosions. I believe that the earliest lesion is thus the superficial erosion, and that the amebae penetrate the deeper layers of the bowel in several places within such an erosion and that this accounts for the observed occurrence of the minute abscesses in clusters.

Even though they are made from apparently typical lesions, not all such aspirations are positive for the amebae. In some instances, aspirations were made on three occasions before the organism was found in the smear or culture. At the same examination, one pipetteful will be positive while others are not. In one instance, though the smears were negative the culture done by Dr. Shaffer was positive. The reason for this fact is not clear, but it stresses the difficulties inherent in the diagnosis of this condition by any available means. It has been our custom to take aspirated material from three or more constellations of ulcers during each sigmoidoscopic examination made for diagnostic purposes or, if no ulcerations are visualized, from three levels of the bowel.

The submucosal pigment spots mentioned above as being observed after treatment appear to be material left submucosally by the healing of the mucosa over the ulcers. In most instances these disappeared within 10 days. In the one case of relapse while carbarsone was being administered, the relapse appeared to be due to recrudescence of ulceration at the site of some of these pigment spots. I was successful in several instances in breaking the mucosa and pipetting the pigment. It appeared to be hematin. The smears and cultures which were made from this material were negative for *E. histolytica*. However, in the observed relapse the impression was gained that the ulcerations had occurred at the location of the pigment spots, and that some of the pigment spots were larger and darker than before, although the mucosa was not broken over them. This observation leads me to suspect that this is the reason why amebiasis is so difficult to treat—namely, that the mucosa will heal rapidly and leave viable organisms submucosally which, if not taken up by the body defense mechanism or eradicated by drug action, will result in relapse. The fact that I have not observed pigment spots more than 10 days post-treatment suggests that the optimal treatment time

for amebiasis would be 25 days, since the ulcerations have healed in 15 days and the pigment spots have not been seen after 10 additional days.

This method of treatment lends itself to out-patient management of amebiasis. Eleven of the 25 cases were treated as out-patients without difficulty. White blood count and urinalysis were done prior to treatment in each case because of the potential toxicity of carbarsone.

The incidence of severe reactions to treatment was considerably less than has been observed following emetine treatment of this condition. The toxic delirium described appears to be due most probably to atabrine. The dermatitis described as due to carbarsone responded promptly to treatment with BAL, and did not recur when treatment of the amebiasis was resumed with atabrine and diodoquin. The nausea and vomiting reported in two cases who were taking the drugs on an ambulatory basis disappeared promptly when the treatment was continued in the hospital. Whether this was due to atabrine or carbarsone is not clear, since both of these reactions occurred in patients taking both drugs simultaneously.

Response to treatment of amebiasis in each instance was dramatic, with the bowel distress usually disappearing within a period of three to four days and remaining clear except for the previously described recurrence of short, sharp episodes of the difficulty, with no change in the bowel appearance or in the stool content. The significance of these episodes is not clear; that others have observed them is manifested from a survey of the literature.^{2, 3, 29} I have explained them to my satisfaction by postulating that a conditioned reflex mechanism is established by some stimulus occurring concomitantly with the actual bowel disturbance due to presence of the amebic ulcerations during the active disease process, and that, after healing of the ulcerations, this stimulus is still capable of causing reflexly the irritable bowel syndrome. From a treatment point of view, such an explanation to the patient, coupled with a careful examination to make certain that the disease has not recurred, seems to stop the incidence of irritable bowel episodes.

The relapse rate of 12 per cent with cases followed as long as this compares favorably with the relapse rates reported in the literature with emetine therapy. Thus, Stewart et al.²⁶ report relapses in 21 per cent of their cases treated with emetine intramuscularly and emetine bismuth iodide, quinoxyl and stovarsol by mouth. Nix⁷ reports a 15 per cent relapse rate following the treatment advocated by Hargreaves,² and 52 per cent following the treatment advocated by Adams.³⁰ A most comprehensive comparative study of the efficiency of various treatment régimes, using sigmoidoscopic examinations as a criterion of therapeutic response, is that of Armstrong, Wilnot and Elsdon-Dew²³ done on the Bantu African. They report 48 per cent failure, with recovery of amebae or presence of ulcers after emetine alone, 42 per cent after diodoquin alone, 26 per cent after combined emetine and diodoquin, and 44 per cent after combined emetine and carbarsone.

In assessing the therapeutic effect of carbarsone from data in the literature, it becomes apparent that there is a difference of opinion, the basis of which is not entirely clear. Thus, Reed, Anderson, David and Leake²¹ report 36 out of 40 patients as being free of the ameba in the stools for a period of four and one-half months after carbarsone treatment. On the contrary, Hummel, quoted by Hargreaves,² is said to have had 25 per cent failure with carbarsone; and Manson-Bahr, in the same article, is stated to have had 100 per cent relapses with carbarsone. Rail²⁵ reports that six cases of 27 had persistent ulcerations after treatment with bismuth kurchi iodide and carbarsone, and six cases of 33 had persistent ulcerations following emetine bismuth iodide, chiniofon and carbarsone therapy. Armstrong, Wilmot and Elsdon-Dew²³ have had similar results with carbarsone, as previously stated. I have personally observed three ulcerative relapses of amebiasis to occur during the time adequate dosage of carbarsone was being given.

SUMMARY

In vitro experiments upon the effect of atabrine, emetine and carbarsone are described, in which atabrine was demonstrated to inhibit the growth of *E. histolytica* in the culture media employed. Atabrine was demonstrated to have no appreciable effect on the streptobacillus of Shaffer and Frye. Attempts to establish cutaneous amebiasis in the cat, kitten and rabbit are described. Granulomatous lesions were occasionally secured which were not thought to represent a suitable method of assessing treatment response. The significant difference in incidence of *E. histolytica* in stools of soldiers returning from the European Theatre of Operations as compared to those returning from the Pacific is discussed, and the widespread employment of atabrine as a malarial suppressive in the Pacific Theatre is suggested as an explanation for this difference. Eleven cases of amebiasis, with visible rectal lesions, were observed for from 10 to 60 days, and the ulcerations were found to be unhealed at the end of the observation period. Ten cases of amebiasis with rectal ulcerations were treated with atabrine first, with healing of the rectal lesions in all instances. They subsequently received carbarsone. Fourteen similar cases were treated with atabrine-carbarsone combination and one with atabrine-diodoquin combination after having had reaction to carbarsone. Relapse rate was 12 per cent in cases followed for from 60 to 395 days by means of smears and cultures of material obtained at recheck sigmoidoscopic examinations. Severe reactions were encountered in two cases, one a dermatitis due to carbarsone, the other a toxic delirium due to atabrine. The relapse rate and reaction rate are compared to reported relapse rates and reaction rates after other forms of therapy, and are found to be favorable. Sigmoidoscopic examination is stressed as a valuable diagnostic aid in amebiasis.

CONCLUSIONS

1. Atabrine is an amebacidal agent which is relatively safe to use in the doses recommended.
2. It should be employed in conjunction with another amebacidal agent capable of eliminating the cysts of the organism.

Acknowledgments. This paper represents the combined efforts of many people who have contributed to this study of amebiasis. The entire professional staff at Fort Knox has been alert to discover cases of amebiasis. Captain Harvey S. Klein contributed a great deal of thought and effort to the in vitro evaluation of atabrine, and conducted much of the search for the *E. histolytica* in the early cases. Dr. James G. Shaffer, Associate Professor of Bacteriology, University of Louisville School of Medicine, has contributed much by way of advice and guidance and has done most of the diagnostic and recheck cultures. Miss Cecilia R. Barthelme has done much of the examination of smears and culture work since Captain Klein's departure. Dr. Klaus Schocken, of the Medical Field Research Laboratory, determined the statistical significance of the incidence of *E. histolytica* in the stools of the returning soldiers. The Army Research and Graduate School furnished the ameba cultures used in the early work, and Dr. James G. Shaffer furnished those employed subsequently, as well as cultures of streptobacillus. Captain J. Richard Compton made valuable contributions to the form and text of the paper.

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ACROMEGALY AND THE HEART: A CLINICAL AND PATHOLOGIC STUDY *

By MILTON R. HEJTMANCIK, M.D., JAMES Y. BRADFIELD, JR., M.D.,
and GEORGE R. HERRMANN, M.D., F.A.C.P., *Galveston, Texas*

HEART disease has long been known as a frequent complicating factor and a common cause of exitus in acromegaly. Only nine years after the recognition of the features of acromegaly by Marie¹ in 1886, Huchard² reported cardiac enlargement in the clinical and autopsy findings of three patients with the disease. Fournier³ drew particular attention to the features of cardiac failure in a series of 25 patients, pointing out the frequent association of cardiomegaly with hypertrophy of all the viscera. Similar reports, consisting usually of one or two cases, have appeared from time to time in the French and German literature, and have been excellently summarized by Courville and Mason.⁴ No conclusive evidence has been brought forth for the etiology and mechanism of such cardiac hypertrophy and myocardial changes.

The size of the heart at times has been enormous, the largest recorded weight being 1,295 gm. by Humphry and Dixon.⁵ Other reported large hearts include weights of 1,275 gm. in Osborne's case quoted by Hinsdale,⁶ 1,200 and 1,140 gm. by Courville and Mason,⁴ and 1,050 gm. by Cushing and Davidoff.⁷ Cardiomegaly is a common but not invariable finding, and the heart weights in acromegaly are usually well below such extreme levels.

In a study of the anamnesis of 100 cases of acromegaly, Davidoff⁸ recorded none of the pathognomonic symptoms of heart failure, although asthenia was noted in 33 per cent. Blood pressures under 120 mm. systolic were noted in 30 per cent of his cases, but appearance of hypertension was not mentioned. Courville and Mason⁴ observed 24 patients with acromegaly; of this group, 18 presented evidence of heart failure, an incidence of 75 per cent. In only three of these cases were elevated systolic or diastolic blood pressures recorded. No specific electrocardiographic changes were described. However, there were noted first notching and widening of the QRS complexes, and later various arrhythmias and T wave changes.

Bartelheimer⁹ has recently studied the circulatory system in a series of 21 cases of acromegaly, of which eight showed the typical full-blown picture and 13 showed evidence of peripheral growth considered illustrative of the *formes frustes* type. Of the 21 cases, 14 had abnormal electrocardiograms, nine with ST depressions in more than one lead and five with intraventricular

* Received for publication December 28, 1949.

From the Cardiovascular Service, University of Texas School of Medicine Hospitals, Galveston, Texas.

Supported in part by a grant-in-aid from the H. H. Weinert Fund for Cardiovascular Research.

conduction disturbances. Abnormalities were more common in the full-blown type; five of the *formes frustes* showed normal tracings. Bartelheimer did not consider that the electrocardiographic changes were due to the presence of hyperthyroidism in eight of his cases, hypothyroidism in one case, and diabetes mellitus in three cases.

Our interest in the heart of the acromegalic individual was aroused by the observation of several patients who presented serious organic heart disease for which no cause other than acromegaly could be found. There seemed a need for a detailed cardiovascular evaluation in a series of such cases, as most reports do not list specific cardiac findings in individual patients. Complete electrocardiographic analyses are few. Many of the cases were reported before the routine use of electrocardiography, while in

TABLE I
Clinical Data in 21 Cases of Acromegaly

Case	Age	Race	Sex	Duration Disease	Associated Disease	Cardiac Failure	Physical Findings Cardiovascular	EKG Findings	Cardiopathy
1 AH	28	W	M	3 yrs.	None	No	BP 124/84. Marked cardiomegaly. Systolic murmurs all valve areas	Complete left B.B.B., with QRS 0.14 sec.	Definite
2 LS	56	W	M	10 yrs.	None	Yes, R and L	BP 102/64. Rate 45 (regular). Slight enlargement. Systolic apical murmur	Not done	Definite
3 JS	27	W	F	?	None	No	BP 108/68. Rate 45 (regular). No enlargement. Distant heart sounds	Not done	No
4 TW	55	C	M	37 yrs.	Gigantism. Leg ulcer	No	BP 114/80. No enlargement. Distant heart tones, with poor quality	Incomplete left B.B.B. QRS 0.12 sec.	Definite
5 DM	40	Mex	M	10 yrs.	Mild diabetes. Bron. asthma	No	BP 138/98. Regular rhythm. No enlargement	Normal	No
6 AG	39	Mex	M	16 yrs.	BMR +52. Mild diabetes	Yes, R and L	BP 118/80. No cardiomegaly	Incomplete B.B.B., not localized. QRS 0.12 sec.	Definite
7 MJ	64	C	M	40 yrs.	BMR -22	No	BP 140/90. No evidence of cardiomegaly	Low T ₁ . Occasional ventricular ectopics	Not definite
8 AMT	28	W	F	14 yrs.	None	No	BP 130/84. No cardiomegaly	Normal	No
9 WHS	28	W	F	4 yrs.	None	No	BP 110/80. No cardiomegaly	Depression 1 mm. ST ₁ and ST ₂ . Neg. T ₃	Suggestive
10 WR	19	W	M	2 yrs.	None	No	BP 150/80. No cardiomegaly	Not done	No
11 JL	41	C	M	?	Hypertension	No	BP 190/130. Moderate cardiac enlargement	Not done	Definite
12 RR	40	C	M	25 yrs.	Diffuse goiter. BMR +23. Mild diabetes. Gigantism	Not definite. Exert. dyspnea	BP 152/90. No definite enlargement	Right axis deviation, tall P ₂ and P ₃ . ST ₃ depressed 1 mm.	Not definite

TABLE I—Continued

Case	Age	Race	Sex	Duration Disease	Associated Disease	Cardiac Failure	Physical Findings Cardiovascular	EKG Findings	Cardiopathy
13* JF	45	W	M	15 yrs.	Hypertension	Yes, R and L	BP 180/100. Marked enlargement. Prominent apical systolic murmur	Left ventricular hypertrophy. Depressed ST ₁ , ST ₂ . Neg. T ₁ , T ₂	Definite
14 JD	47	W	M	23 yrs.	Hypertension	Not definite. Exert. dyspnea	BP 180/110. No definite enlargement. Distant, muffled heart tones	Left ventricular hypertrophy. Depressed ST ₁ , ST ₂ . Neg. T ₁ , low plus T ₂	Definite
15* WOB	49	W	M	16 yrs.	BMR -10	No	BP 112/78. Slight enlargement. Distant heart tones	Incomplete B.B.B., not localized. QRS 0.11 sec. Neg. T ₁	Definite
16* EMT	41	W	F	14 yrs.	Hypertension. Adenoma thyroid. BMR +36. Mild diabetes	Yes, R and L	BP 156/90 to 180/120. Marked enlargement. Systolic apical murmur	Left bundle B.B. QRS 0.13 second	Definite
17 RW	59	W	F	?	None	No	BP 156/70. Heart enlarged. Tones distant, tic-tac quality. Gallop at base	Not done	Definite
18* HQ	45	W	F	20 yrs.	Hypertension	No	BP 220/115. Marked cardiomegaly	Not done	Definite
19 MMN	63	W	F	15 yrs.	None	No	BP 115/74. No cardiomegaly. Sounds distant	No abnormality. Occasional ventricular ectopics	No
20 VR	41	W	M	20 yrs.	Hypertension. BMR +40	Yes, R and L	BP 130/100 to 150/120. Marked enlargement. Gallop rhythm	Incomplete left B.B.B., QRS 0.11 sec. P-R 0.24. Depressed ST ₁ , neg. T ₁ , low T ₂	Definite
21 JT	62	W	M	40 yrs.	Diabetes, mild	No	BP 140/88. Moderate enlargement. Distant sounds	Left axis deviation. Neg. T in I and IVF	Definite

* Necropsied cases.

other reports the electrocardiographic changes in individual cases were not described. Examination of the available pathologic material was also considered desirable, in an attempt to arrive at the structural bases for the functional abnormality.

THE PRESENT STUDY

A survey has been made of the cardiovascular status of 21 established acromegalics seen at the University of Texas Medical Branch in the past 25 years. Only classic acromegalics were included. The records of five additional patients in whom the diagnosis was not considered well substantiated were discarded. Electrocardiograms were available on only 15 patients, because some were admitted before electrocardiography had become a common procedure. In other cases there were negative physical cardiac findings, or the patients were in a terminal state. X-Ray studies of the heart were performed on most of the patients. Necropsy protocols and micro-

TABLE II
Heart Disease According to Age Groups

Age	No. Patients	Cardiopathy
10-20	1	0
20-30	4	1
30-40	1	1
40-50	9	7
50-60	3	3
60-70	3	1

scopic sections were reviewed in four of the five patients who died during hospitalization.

Table 1 presents a summary of the clinical and electrocardiographic findings in each case, with particular reference to the cardiovascular system. Although there is usually an equal sex distribution, 14 of our patients were males and only seven were females. The ages varied from 19 to 64 years. Table 2 shows the clinical evidence of cardiopathy in the various age groups,

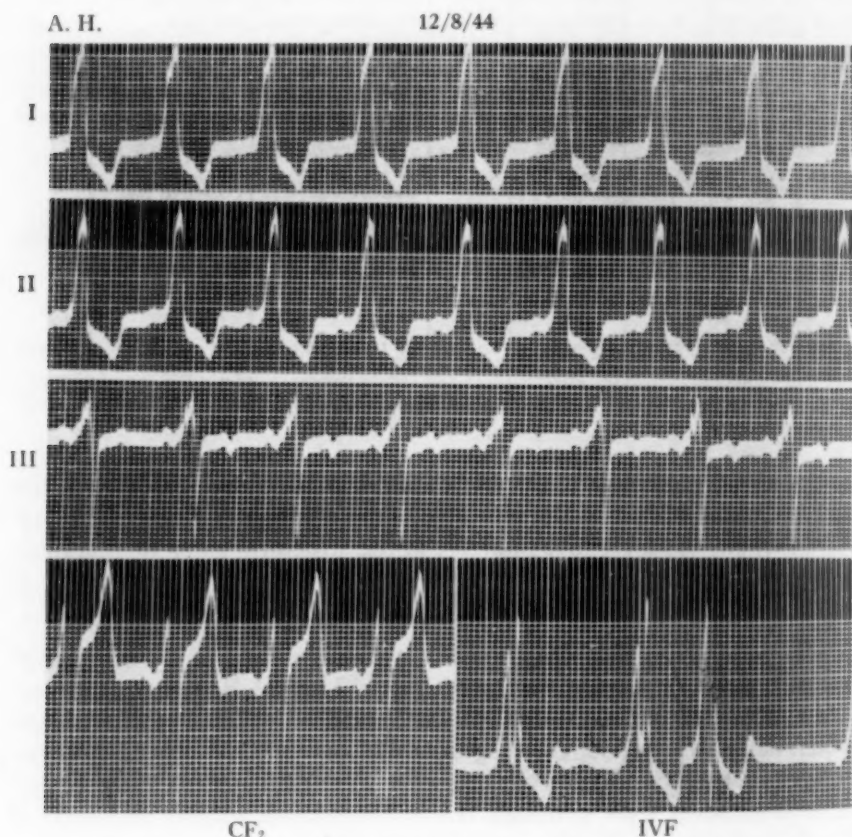


FIG. 1. Electrocardiogram of A. H., a 28 year old white male with no demonstrable cause for cardiopathy other than acromegaly. The tracing shows complete left bundle branch block.

dominant in the fifth decade. Duration of the disease in certain instances was not obtainable. However, onset was usually in the third decade.

Of the 21 patients, 13 had clinical evidence of cardiopathy, and five were admitted in frank congestive heart failure. Two patients complained of exertional dyspnea that was believed to represent transient left ventricular failure, but they showed no definite signs of cardiac decompensation. One additional patient was considered to present suggestive evidence of cardiac

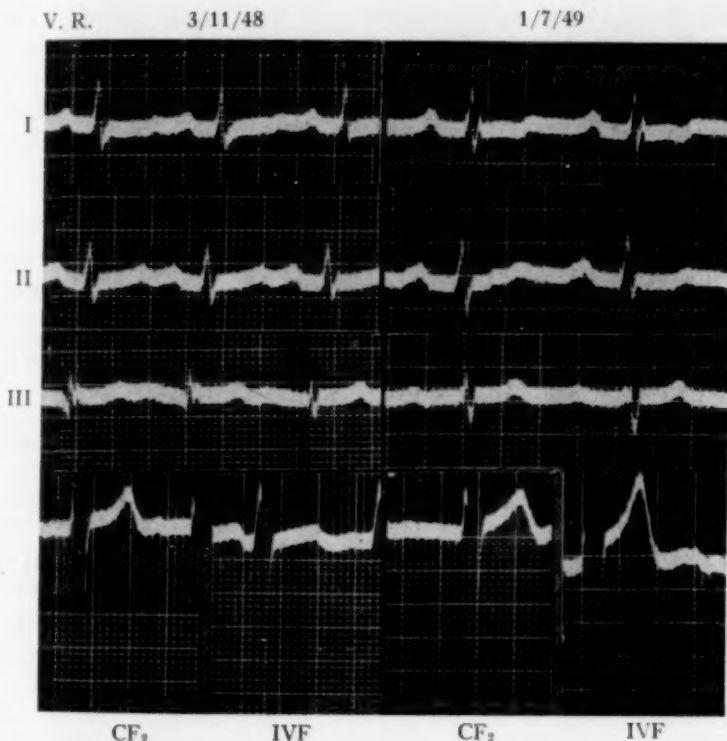


FIG. 2. Electrocardiograms of V. R., a 41 year old hypertensive white male with acromegaly, before and after digitalization. There is impaired intraventricular conduction of 0.11 second, localized to the left by precordial leads not shown. The P-R interval is prolonged in both tracings, and there are suggestively abnormal ST segment and T wave changes, particularly in Lead I.

abnormality because of ST depressions in the electrocardiogram. We were unable to correlate duration of symptoms with signs of heart disease. Three patients with symptoms of 10 to 15 years' duration had apparently normal cardiovascular systems.

Of the 15 patients on whom electrocardiograms were available, nine were considered to have abnormal tracings. The most frequent abnormality was impaired intraventricular conduction, which was noted in six patients. Two of these showed complete left bundle branch block; one was a normo-

tensive 28 year old white male with no other demonstrable cause for cardiopathy (figure 1). The other four patients with intraventricular conduction disturbances had an incomplete bundle branch block, the QRS complexes measuring 0.12 second in two and 0.11 second in two. The block was localized to the left bundle in two of these patients by multiple precordial leads. One, a 41 year old white male with hypertension, presented in addition a prolonged A-V conduction time of 0.24 second. His electrocardiograms are reproduced in figure 2. The pattern of left ventricular hypertrophy was noted in two additional patients with hypertension. The one remaining abnormal electrocardiogram showed negative T waves in Leads I and IVF.

Repeated blood pressure determinations were made on many of the patients. These varied considerably from time to time, and the higher con-

TABLE III
Summary of Pathologic Material

Case	Heart Gm.	Liver Gm.	Spleen Gm.	Kidneys Gm.	Aorta and Coronaries	Microscopic Findings, Heart
13 JF	"Mkdly enlarged"	No other tissues permitted			Aorta dilated with few areas atherosclerosis. Coronaries normal	Marked hypertrophy of muscle fibers with fragmentation
15 WOB	450	2600	300	160 (R) 130 (L)	Rare small atheromatous patches in aorta. Coronaries patent	Hypertrophy of myocardial fibers with fragmentation
16 EMT	1140	3050	390	310 (R) 320 (L)	Few areas atherosclerosis of aorta. Small patch atherosclerosis left coronary artery, but coronaries patent	Marked hypertrophy muscle fibers, with fragmentation and loss of striations. Marked diffuse fibrous hyperplasia
18 HQ	680	3500	180	300 (R) 300 (L)	Marked atherosclerosis aorta with plaques. Moderate sclerosis coronaries, but patent throughout	Hypertrophy of myocardial fibers. Moderate increase in fibrous tissue

firmed levels are recorded in table 1. Six of the patients had blood pressures in hypertensive levels, i.e., above 150/90. All six showed cardiac enlargement, and three were in obvious decompensation. Electrocardiograms on four of the six hypertensive patients were available. All four were abnormal, two presenting disturbances in intraventricular conduction and two a left ventricular hypertrophy pattern.

An associated hyperfunctioning of the thyroid gland was found in four cases, two of which also had hypertension. Electrocardiograms were taken in all these cases, and three showed definite clinical and electrocardiographic signs of heart disease. Two patients had basal metabolic rates of minus 22 and minus 10, one of these showing an incomplete bundle branch block. Of five diabetics in the group, all with electrocardiographic studies, three pre-

sented definite evidence of cardiopathy. One of the patients (EMT) with impaired glucose tolerance also had hypertension and a diffuse goiter with basal metabolic rate of plus 23 per cent. This patient died in cardiac decompensation. Her electrocardiogram demonstrated complete left bundle branch block.

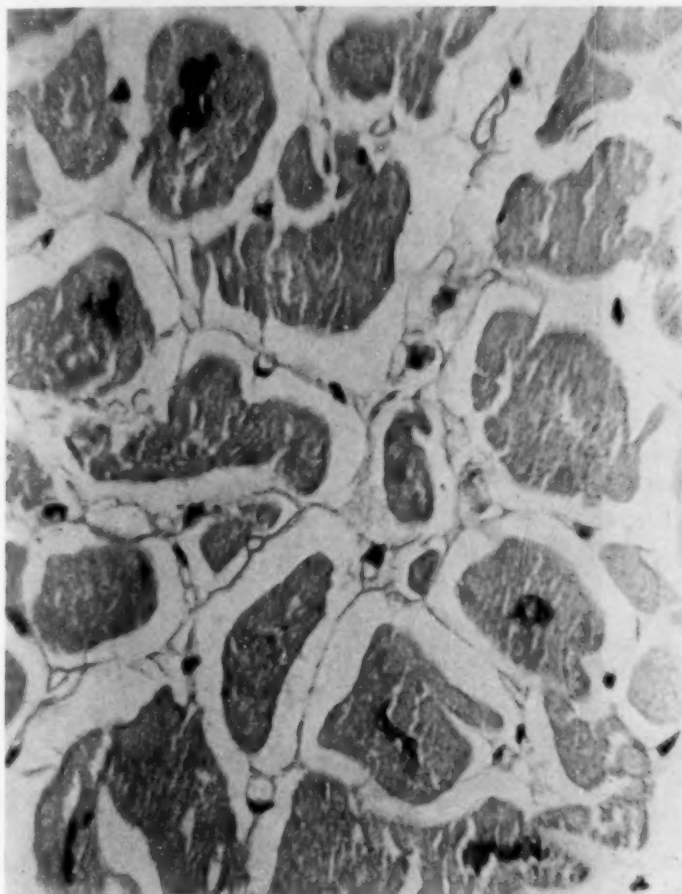


FIG. 3. High-power magnification of representative section of heart of W. O. B., a 49 year old white male with acromegaly and normal blood pressure. The hypertrophic myocardial fibers are surrounded by lacy, interconnected strands of hyperplastic fibrous connective tissue. H & P, $\times 502$.

Autopsy studies, summarized in table 3, were performed on four of five patients who died during hospitalization. Three of the four had an associated hypertension, of which two died of right and left ventricular failure. One (WOB) died of a hemorrhage into the pituitary tumor. The cause of death of the remaining patient (HQ) was cerebral thrombosis. One necropsy was limited to the heart. In each case there was cardiac

hypertrophy, this being enormous in one patient (EMT), with a heart weight equal to the fourth largest heart reported in acromegaly. A moderate amount of atherosclerosis of the aorta was seen in all our autopsied

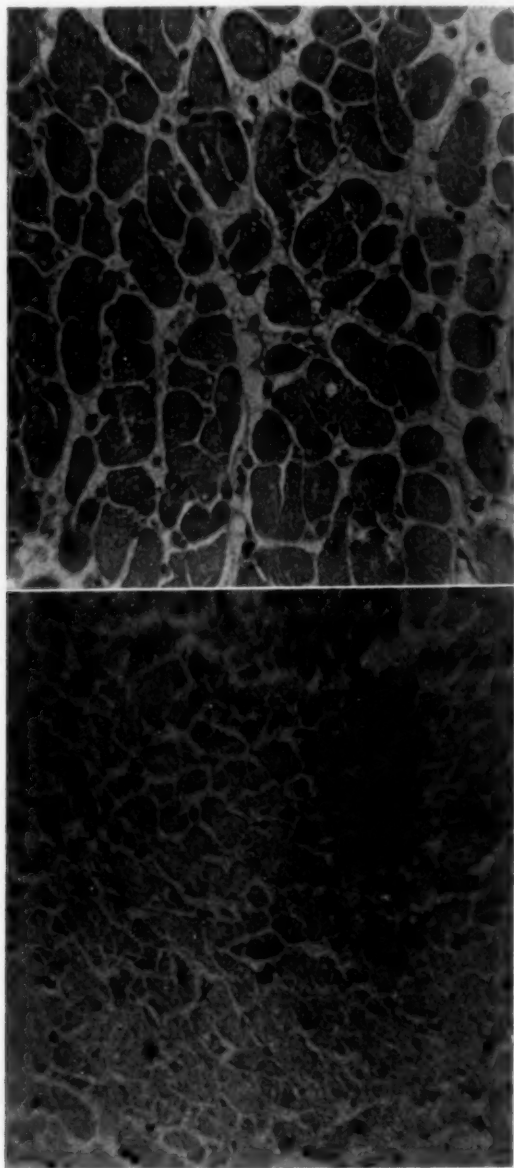


FIG. 4. Cross sections of heart of H. Q., 45 year old acromegalic white female (above), and comparison with normal myocardium (below). Note the fiber hypertrophy and diffuse interstitial fibrosis in the acromegalic heart. Same magnification, H & P, $\times 190$.

cases, but the coronary arteries were patent throughout. No valvular deformities were noted.

Microscopic examination showed marked hypertrophy of the myocardial fibers in all of the sections. Fragmentation of the muscle fibers with loss of striations was frequently noted. A conspicuous diffuse hyperplasia of interstitial fibrous connective tissue was evident in two cases. This was very marked in one patient (WOB), and a representative field is reproduced in figure 3. The lacy fibrous strands were seen to interweave and separate each individual myocardial fiber. The fibrosis was less marked but definitely evident in another case (HQ). The hypertrophied muscle is compared with a section of normal myocardium in figure 4. No inflammatory cell infiltration or conspicuous vascular disease was evident in any of the sections.

DISCUSSION

The frequency with which cardiopathy is noted in acromegaly appears to depend largely on the type of institution in which the patient is studied. In a neurosurgical center, there is emphasis on treatment of the pituitary tumor, and the patients are often seen earlier in the course of the disease; hence, cardiac complications have been encountered less frequently than on the medical wards, where manifestations of myocardial insufficiency may actually have occasioned hospitalization. Such patients are then treated in the end-stage of their disease, with the cause of death often cardiac failure.

There are several possible mechanisms for the impairment of cardiac efficiency and the development of heart disease in acromegaly. Generalized splanchnomegaly is one of the classic features of the disease, and the heart is known to share in the visceral enlargement. In most cases of heart disease, hypertrophy of the myocardial fibers is usually a secondary, compensatory mechanism striving to maintain energy output adequate to meet the demands of the tissues. However, acromegaly appears to be one condition in which the heart muscle may enlarge primarily under hormonal stimulus of the anterior pituitary, as postulated by Amsler.¹⁰ Furthermore, as Courville and Mason⁴ have pointed out, the abnormal growth of other body organs and tissues probably imposes an increased work demand on the heart. Hypertrophy may be partially compensatory because of poor functioning of the abnormally stimulated muscle cells. Such mechanisms are probably responsible for the instances of cardiac enlargement in which microscopic sections show only myocardial hypertrophy, and where no other known cause, such as hypertension or atherosclerosis, exists.

The fibrous tissue proliferation produced in the skin by the eosinophilic process in the anterior pituitary is well known (Kraus¹¹). Although one would also expect proliferation of interstitial fibrous tissue in other organs, these changes have been described only occasionally in the heart. Cushing and Davidoff⁷ reported a marked diffuse increase in supporting connective

tissue in the heart in one of their patients. Fibrosis and cellular infiltration were also noted in the hearts examined by Courville and Mason.⁴ An increase in interstitial fibrous tissue strands was observed in two of the four cases reported by Goldberg and Lissner,¹² but both of these showed, in addition, sclerotic coronary arteries. One of our cases showed marked diffuse connective tissue proliferation in the heart, and another showed this change to a lesser degree, each without coronary sclerosis sufficient per se to explain these changes. However, no cellular infiltration was observed. Fibrotic tissue proliferation undoubtedly impairs the function of the myocardium. It may also disturb the process of normal impulse propagation, and thus be responsible for the frequency of impaired intraventricular conduction as recorded in the electrocardiograms in this series.

Sternberg¹³ and Hinsdale⁶ have described the arteries in acromegaly as being dilated and thickened, and atheromatous changes were occasionally noted. Our cases showed mild to moderate intimal sclerosis of the aorta, but the coronary arteries were wide and patent. Coronary artery sclerosis is an etiologic factor in the cardiopathy of some acromegalics, but is found only occasionally and cannot be regarded as the usual cause. Courville and Mason⁴ were unable to correlate it with the cardiac hypertrophy of acromegaly.

Davidoff and Cushing¹⁴ reported diabetes mellitus in 12 per cent of a group of 100 patients with acromegaly, an incidence later raised to 17 per cent in a follow-up study by Coggeshall and Root.¹⁵ It was present in five of our 21 cases, an incidence of 23.8 per cent. Although the cardiovascular complications of diabetes mellitus are well established, the high incidence of cardiac disease in acromegaly cannot be attributed to the diabetic state either in past reports or in this study.

Thyroid enlargement and an elevated basal metabolic rate have frequently been observed in acromegaly. Cushing and Davidoff¹⁶ found an elevated basal metabolic rate in 49 out of 72 cases. Exacerbations and remissions usually occur, due to changes in the production rate of the thyroid-stimulating factor in the anterior pituitary hormone. Davis¹⁷ noted thyroid enlargement in 50 per cent of 166 cases of acromegaly. Although follow-up studies were not available, he was impressed with the possibility of persistent hyperthyroidism as a cause of myocardial insufficiency in such cases. Despite a normal basal metabolic rate at the time of study, it may have been elevated in the past and have produced cardiac damage at that time.

Hypertension is not usually considered a part of the clinical picture of acromegaly, although it has been observed in sporadic cases. Humphry and Dixon⁸ reported isolation of pressor substances in the urine in an acromegalic with hypertension and an enlarged heart, but they did not believe it was pituitary in nature. Only three of the 24 patients of Courville and Mason⁴ presented hypertension. Bartelheimer⁹ noted sporadic hypertension in his cases, and attributed it to concomitant hyperfunction of the baso-

phil portion of the anterior pituitary lobe. He suggested that stimulation of the adrenal cortex through this mechanism might produce transitory rises in blood pressure, but only rarely a permanent hypertension. Selye,¹⁸ apparently on theoretic considerations, related the "cor bovinum" in acromegaly to the rise in blood pressure, but in many cases with large hearts no such association has been noted. Six of our 21 patients had hypertension, an unusual incidence of 28.6 per cent. Hypertension may represent, as an elevated basal metabolic rate, a temporary state, and may be "burned out" at the time of admission. This occurred at the last admission of one of our cases, who had been followed over a period of 10 years. Although the association of hypertension with acromegaly remains to be fully evaluated, it can be safely concluded that acromegalics tolerate hypertension poorly. It is in this association that the extremely large hearts and early cardiac decompensation are sometimes found.

SUMMARY

1. An analysis is made of the cardiovascular findings in 21 patients with acromegaly, in four of whom necropsy was performed.

2. Thirteen of the 21 patients had clinical evidences of heart disease. Five were in frank cardiac decompensation, and two had transient episodes of left ventricular failure. Nine of 15 patients with electrocardiographic studies showed abnormal tracings, with impaired intraventricular conduction in six and left ventricular hypertrophy pattern in two. Six patients had hypertension, four had elevated basal metabolic rates, and five had diabetes mellitus.

3. Pathologic study of four patients demonstrated cardiac enlargement. The heart in one case weighed 1,140 gm. Microscopic sections showed hypertrophy of the myocardial fibers, with conspicuous diffuse fibrous tissue proliferation in two cases.

4. Direct effect of the hormone of the anterior pituitary seems to be the predominant factor causal of cardiac hypertrophy and interstitial fibrous tissue proliferation. Increased work demand by other tissues stimulated to abnormal growth by hormonal action is contributory, as is occasionally thyrotoxicosis and/or impaired glucose metabolism.

5. The integration of sporadic hypertension in the disease process, and the part it plays in the pathogenesis of cardiopathy, demand further evaluation. Certainly, hypertension appears poorly tolerated by the heart of the acromegalic.

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SOME REFLECTIONS ON MEDICAL EDUCATION *

By WILLIAM S. MIDDLETON, M.D., F.A.C.P., *Madison, Wisconsin*

MEDICAL education had its origin in the priesthood of antiquity. For many generations the shaman, or priest, and the practitioner of the healing art were one and the same individual. Under the Hippocratic oath, the knowledge of the medical skills was imparted only to physicians and to the sons of physicians. Chomel termed this the traditional method of medical instruction. In the evolution of Greek culture, medicine was eventually separated from the priesthood. The first medical school at Alexandria was founded by Alexander of Macedonia. Notable medical figures, as Herophilus, Erasistratus and Galen, trained in this school. With the Roman conquest of Egypt, the school at Alexandria was disbanded. Interestingly, the church bridged the gap until the establishment of the next formal medical school at Salerno in the Ninth Century A.D. The monks at Monte Cassino assiduously copied ancient medical works, while at St. Gall the first medicinal botanical garden was maintained.¹

The torch of medical education lighted at Salerno was kept bright for at least four centuries, but its decline dates from the Thirteenth Century, when the medical leadership passed in turn from Bologna to Naples to Montpellier to Paris. The doors of the University of Salerno were eventually closed by Napoleon in 1811. True academic tradition in pageantry and form dates from the University of Paris. The influence of the church in medicine waned very perceptibly when first surgery and then all forms of medical practice were denied the priesthood. In France, surgery was separated from medicine and taught at the Collège du St. Côme.¹ In turn, Leyden, Edinburgh and London gained ascendancy in medical education in the late Seventeenth and Eighteenth Centuries. The first medical school in North America was established as the Medical Department of the College of Philadelphia in 1765. Its founders, John Morgan and William Shippen, Jr., were both graduates of Edinburgh.

Before the establishment of the medical school in Philadelphia, the apprentice system of medical education prevailed. Among the most notable of the Philadelphia preceptors were John Kearsley, Sr., and John Redman. While formal medical education showed a mushroom growth in the Nineteenth Century, the pattern of medical apprenticeship persisted in varying degrees throughout this period. The opportunity to read in an established physician's office was a coveted method of introduction to the study of medicine almost to the end of the Nineteenth Century in this country. True, the house pupils were frequently required to perform menial duties, but the

* Being in substance the address given at Regional Meetings in Trenton, New Jersey, and Chapel Hill, North Carolina. Received for publication March 28, 1951.

From the Department of Medicine, University of Wisconsin Medical School.

intimate contact with practicing physicians in the office and sickroom earned incalculable dividends in the attainment of the art of medicine.

The formula for the first organized courses of medicine in America differed in no wise from the European or the British pattern. Classroom lectures and demonstrations were the rule. Personal dissection by the medical student was exceptional, and prosectors were commonly employed by the professors of anatomy to demonstrate either the actual dissection or prepared anatomic specimens. Private courses were conducted not only by independent teachers but also by occupants of the respective chairs in the medical schools. So limited was the scope of medical knowledge that the short course of winter lectures was repeated in the second year, and only two such courses were required for graduation. Not until 1872 was the course lengthened to three years of five months each, over the protest of many members of the profession. The four-year course in medicine dates from 1894-95.

The requirements for admission to medical schools had undergone an almost imperceptible improvement before the Flexner report (1910). Since that time, there has been a distinct trend toward vocational preparation. Indeed, in recent years the more vociferous sciences have seriously crowded the humanities from the scene. A majority of medical schools require three years of premedical preparation. Of 90 essential credits over this period, some 70 odd are actually required for admittance by most institutions. With the science subjects in the ascendancy, chemistry is finding ever increasing weight.

The medical curriculum, like Topsy, "has just grown." Neither its length nor its content has been subjected to serious functional change in the past 40 years. In its organization, too frequently compartmentalization prevails by reason of the overweening ambitions of special departments and skills. The movement toward overspecialization in medicine has made its impact felt even upon the undergraduate training of medical students. In many instances, highly refined specialties are taught to the medical student by teachers whose perspective is seriously distorted by their limited field of interest and vision. Mechanization has supplanted clinical acumen and judgment in many quarters. A medical wag has said, "Here lies the body of Hiram Smythe, born a man, died a gastroenterologist." Undoubtedly, this system has certain elements of strength in offering to the medical student in his formative period the latest knowledge within specific areas of medical endeavor. By the same token, such a student, pursuing this development to his ultimate practice of the profession, could never be expected to see the patient as a whole, the host of a disease, from such a detached approach.

The remedies for the present situation in medical education should begin with the college program. It is eminently unfair from a psychologic as well as a practical standpoint to term this period of preparation "premedical." Rather, it should be "pre-professional," or general collegiate training with

special weight, but without vocational implication. Medical administrators appreciate the mental hazard to even our superior aspirants for medical training when the tag of "premedical" is placed upon them from their matriculation in college. If, in the course of the next few semesters, other aptitudes present, or a lack of proficiency in special sciences emerges, a serious dilemma confronts the unfortunate student. In all probability the designation of a "pre-professional" course will be the early answer to this problem. In the interest of sound educational tenets, the entire college curriculum should be reviewed with a thought to broadening its base. In general, medical educators are agreed that foreign languages should be eliminated as required subjects. A minority of students, those with either a proper background or the prospect of a future in medical research or academic fields, should be encouraged to acquire a good working knowledge of one or more foreign languages. For the vast majority, the current requirement of two years of college French or German is a sheer waste of time. The classical languages, Latin and Greek, offer much sounder educational disciplines, if this be the objective. Currently, the natural sciences have usurped a lion's share of the college curriculum in the preparation for medicine. In the interest of broadening the product of such training, the humanities, social sciences and psychology should be materially increased at the expense of the natural sciences. Furthermore, the natural sciences may properly be subjected to careful study. They should be taught as living sources, not as unsavory memory disciplines. The mere accumulation of isolated facts for regurgitation in more or less digested form at examination is not a measure of true education.

The next consideration, namely, that of the selection of students for admission to the medical school, is a very sensitive one. Particularly is this true when one represents a state-supported medical school in which preference must be given to residents of the state in the order of their academic accomplishment. Nevertheless, it is possible that such an experience may more properly qualify one for fair judgment in this matter. After 40 years in academic life, I find it increasingly apparent that qualities of character and judgment are more important than mere intellectual attainment in the practice of medicine. Conversely, it should be equally evident that there is no logical basis for the assumption that, because an individual has unusual intellectual endowment, he need be lacking in these most significant attributes of the practicing physician. Since the function of the medical school is primarily the production of physicians, in the ideal situation one would leave only a small secondary space, constituting not more than 10 per cent of the elected, for the potential research prospects. Undoubtedly this would be the more difficult group to select, and a 50 per cent error would leave the very high figure of 5 per cent of prospectively productive graduates in the field of medical research.

A careful evaluation of the medical curriculum, with the possibility of its rational revision, has long been overdue. Lest this circumstance be

deemed a measure of complacency, it should be indicated that the medical courses have been continuously subjected to minor changes over the past generation. Indeed, among the professional disciplines, medical education is deemed the most progressive. Yet we cannot accept this position as satisfactory. Let us first look to our objective. The late Professor William H. Welch, of the Johns Hopkins University, related the following experience to me: "Armed with letters from Doctors' Janeway and Osler, I presented myself to Dr. James Mackenzie on an early visit to England. He read the notes and then turned to me and said, 'I am well acquainted with some of your work in bacteriology and pathology, but are you the Welch who has had something to do with medical education at Baltimore?' When I admitted that I might be he, Dr. Mackenzie continued, 'Well, you are making the biggest mistake in the world.' When I protested mildly and asked whether he had a basis for such a statement, he said, 'Yes, when I was a medical student, we had a professor who took the men out of the clinics and classrooms and put them in the laboratories, and even sometimes took them out of the wards and put them in the laboratories.' I ventured to ask what was the result of this practice. Dr. Mackenzie retorted, 'I came out of the medical school knowing no medicine.' I interjected, 'And knew that you knew none and wished to learn more?' 'Yes,' he said, 'and I wished to learn more.' 'Then,' I said, 'Dr. Mackenzie, you have had the finest medical education I have ever heard of.'"

From many quarters you will encounter proposals for the integration and correlation of medical instruction. The movement for the vertical coordination between the preclinical and the clinical subjects is growing throughout the medical world; but there has been little effort to carry this principle into a horizontal integration at the preclinical levels. For a generation, the basic sciences were taught as abstract sciences, and any suggestion of practical application was offered apologetically. The leaders in anatomy, histology, physiology and physiologic chemistry, particularly, felt that they were losing caste among their kind if their respective subjects had a popular appeal to the students. Without prostituting their ideals, and without seeking vocational levels, such teachers should give increasing thought to the potentialities of correlating information among the related subjects, so that the student is confronted with a living unit. The opportunity for effective integration is even greater in the area of medical microbiology and pathology. The elimination of detailed technic, as of dissection, staining reactions and cultural characteristics, except in the interest of a cohesive design, should be seriously considered in all subjects. The routine lecture is a relic of bygone generations. Occasionally there are special fields in which the instructor may have unusual grasp or facility which will offer insight and direction to the medical student. On the other hand, the mechanical transfer of the pearls of wisdom from the instructor's lips to the notebook of the student is one of the most wasteful of pedagogic procedures.

Unfortunately, about 85 per cent of students at all levels must be spoon-fed, and only 15 per cent (a liberal estimate) will think for themselves. Certain subjects, as pathology, are replete with theories. If this preferred 15 per cent might alone be stimulated by the theoretic considerations, the time and effort of the majority as well as of the instructor would be spared. To this minority group should also be afforded the stimulating experience of opportunity for the observation and experimental study of phenomena uncovered by their mental curiosity. Revitalization of the basic sciences by the appropriate introduction of clinical subjects is an expedient that is now widely and commendably employed. Even the most uninspired student might well be stimulated by this method, and would grow apace as source references are cited and explored. The introduction of psychobiology and medical psychology into the preclinical period is a wholesome sign of the times, but the social sciences have been seriously neglected in this newer development. Adequate exposures to the existing philosophies and practical examples of their operations will better prepare the medical student for the realities of a modern world when he is introduced to the practice of medicine. Above all, time for contemplation should be afforded. Perhaps no better means to this end than the continuance of non-science electives into the medical school can be recommended. Even in education, a change of pace is an effective device.

Ideally, there should be no sharp division between the preclinical and the clinical disciplines of the medical student. Certainly he is in a much better position for thinking in terms of basic sciences when confronted with the clinical problem, and the converse is patent. Cross fertilization by an interchange of instruction among representatives of the preclinical and clinical fields insures a mutual advantage to both the students and the staff. In this day of overspecialization, it is most important to avoid a segmentation of medicine by the exposure of the student to the technic of specialists. The medical curriculum, particularly in the clinical fields, has grown by accretion. Much of the current crowding of the so-called clinical years depends upon this circumstance, which has obtruded itself without thought to its pedagogic unsoundness. For example, radiologic considerations may be attached to a series of clinical subjects if the student be given only a very slight insight into the principles involved in this highly specialized field. Certainly, undergraduate medical students should not be expected to acquire a profound mastery of these technical subjects. To insure the best clinical approach in the ultimate product, the physician, the patient should be presented as a unit. The patient, as the host of the disease, will be subjected to many forces. The student who is introduced to the consideration of medicine with due emphasis upon the effects of heredity, environment, nutrition, sociologic and economic conditions, will be much broader beamed than one who approaches his ultimate clinical problems from a series of tangential specialties. From the inception of the clinical years at the University of Wisconsin Medical

School (1925), a coördinate course of medicine and surgery has been afforded. Wherever possible, all hours and facilities are pooled. Every skill that impinges upon the ultimate management of a given disease is utilized in continuity. For example, if foreign bodies in the tracheobronchial tree be under consideration, in sequence the pediatrician, roentgenologist and otolaryngologist will discuss the subject with the class. Effective as is such a simple device, periodically the members of the faculty must be briefed as to their respective responsibilities toward the total effort.

Singularly, medical educators have assumed that teachers are born. Until relatively recent years, there has been no studied effort to establish the validity of this position. Yet the technics of education have grown apace. It is high time that we invite specialists in the field of pedagogy to advise us in this matter. Growth in clinical medicine depends upon painstaking attention to details. Osler wrote, "To study the phenomena of disease without books is to sail an uncharted sea. While to study books without patients is not to go to sea at all." At the bedside, then, with careful supervision and increasing responsibilities, the student lays the foundation for his ultimate development to clinical maturity. The instructor has the added opportunity of inculcating in the student at this malleable period an appreciation of his reciprocal responsibility to society. In 1926, the late Dean Charles R. Bardeen introduced the Wisconsin Preceptorial Plan, which attempts to recapture the advantages of the old house pupil-preceptor relationship. By the expedient of extending the normal academic year of 36 weeks to 48 weeks in the senior year, an added quarter is gained to the student. During this period he is assigned to a recognized clinician in one of 15 centers in the state. A single physician is made the responsible preceptor, although he may have any number of associates. Dr. Bardeen's design was to permit the student at this stage in his development to look over the shoulder of a tried clinician, and to observe his manner of handling the medical situation at its source. For the first time, these medical students realize the impact of environment upon disease expressions. At this very early stage in their development, their responsibility to society and many other sociologic, ethical and economic implications are brought into relief. In our judgment, the extramural preceptorship is one of the most effective elements in the educational discipline of the medical student.

With this background, Professor Welch's philosophy of medical education must obtain. No student will leave the medical school with a sense of the fulfillment of his training. Brown has written, "Education is not something that is wrapped up and handed to the graduate rolled up in his diploma. Education is not a thing at all, but a process." May you enjoy this process to the end of your days; for then will your years be full and your life contented.

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CASE REPORTS

BACTERIAL ENDOCARDITIS WITH EMPHASIS ON THE ESCHERICHIA-AEROBACTER GROUP AS THE CAUSATIVE AGENT: REPORT OF A FATAL CASE*

By C. STEWART WALLACE, M.D., F.A.C.P., Ithaca, New York

IN 1873 Lancereaux gave the first modern clinical description of bacterial endocarditis.¹ From then until a few years ago, interest in the disease was largely academic. With the advent of modern chemotherapeutic agents, new interest was created in the treatment of bacterial endocarditis. The result is one of chemotherapy's greatest triumphs. A majority of the cases caused by organisms sensitive to antibiotics are being cured. A smaller number have failed to respond.

A wide variety of organisms have been described as etiologic agents in bacterial endocarditis. Various authors have estimated that the streptococcus is responsible for 90 to 95 per cent of all cases of the disease.^{2, 3} In the remaining cases, many different organisms are reported. Reports of cases with individual bacteria from this small group are indeed rare, most of them being concerned with gram-negative bacilli, of which *Hemophilus influenzae* accounts for the largest number. Unidentified gram-negative bacilli and organisms of the Escherichia-Aerobacter group are also occasionally reported in the literature. It is this latter group of organisms, as the etiologic agent, that has been selected for discussion in this report.

The literature on endocarditis with organisms of the Escherichia-Aerobacter group is exceedingly sparse. One finds but 17 reports of cases. Of these, *Escherichia coli* was responsible for 13,^{4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15} but *Aerobacter aerogenes* for only four.^{15, 16} Several of these cases, although reported as due to organisms of this group, are not definitely proved, as the authors do not describe demonstration of the typical organisms in the bacterial vegetations by staining or by culture.^{5, 6, 7, 8, 9} Of all the cases reported, only one has recovered.¹⁵

In his original description of *Bacterium coli*, Escherich^{17, 18} noted the occurrence of two types. One was *Bacterium coli* (now called *Escherichia coli*), which formed relatively long rods, was motile and clotted milk slowly. The other was *Bacterium lactis aerogenes* (now called *Aerobacter aerogenes*), which formed shorter plumper rods, was more motile and clotted milk more actively. The use of a relatively small series of fermentation tests and other specific tests serves to separate these organisms from the other coliform bacilli. In the past, doubt regarding the pathogenicity of these organisms was expressed by several authors, particularly their rôle in bacterial endocarditis. Blumer² in 1923, in a discussion

* Read at Western New York Regional Meeting, American College of Physicians, October 20, 1948.

Received for publication April 30, 1949.

of the etiology of bacterial endocarditis caused by organisms other than the streptococci, observed: ". . . So few other organisms have been described during the era of modern clinical bacteriology that we are constrained to believe that some, at least the older observations, concern accidental contamination or terminal invaders rather than the true cause of the disease." Many have held that these organisms have the rôle of secondary invaders. However, in the reported cases the pathologic changes point to no other disease, and the isolation of the organism in pure culture strongly suggests a causal relationship.

Topley and Wilson¹⁹ express the opinion that the majority of the lactose-fermenting coliform bacteria appear to be nonpathogenic under ordinary conditions. *Escherichia coli* is a normal intestinal organism, whereas the normal habitat of *Aerobacter aerogenes* is on soil and plants, although it may be found infrequently in the intestine. Under abnormal conditions, these bacteria may cause acute or chronic infectious lesions of the urinary tract, the gastrointestinal tract, the female genital tract, the biliary tract, or may be a contaminant in wounds. These infections may lead to fatal septicemia. The reasons for the sudden pathogenicity of these usually harmless saprophytes remain obscure.

Hill and Seidmann,²⁰ in a report of coliform bacteria in genitourinary tract infections, point out the relative abundance of *Aerobacter* strains in the urine. They show that the incidence of *Aerobacter* strains in urinary tract infections is greater than that of its normal presence in the intestine. They are of the opinion that, if the source of the infection is intestinal, it is possible that the fecal organisms which find their way into the urine respond to some selective action in the genitourinary tract which operates to favor the genus *Aerobacter* over *Escherichia*. In the bowel, *Escherichia* far outnumber *Aerobacter*.

In a recent study by Wilhelm and Orkin²¹ of the incidence of *Aerobacter aerogenes* infections of the urinary tract, the following observations were made. In 211 consecutive admissions to the genitourinary service of the Beth Israel Hospital in New York City during 1940-41, *Aerobacter aerogenes* was found in 6.6 per cent of the urine cultures. Using the same bacteriologic methods, a series of 350 consecutive admissions between 1945 and 1948 was also studied. This group revealed 45.7 per cent of cases of *Aerobacter aerogenes* infection recovered. In their 12 cases in 1940-41, there were no fatalities and no positive blood cultures. In the 1945-48 series of 126 cases, there were four who were gravely ill with positive blood cultures, and one who died. They also observed that 88 per cent of the organisms recovered in the latter series were resistant to streptomycin. It was their opinion that *Aerobacter aerogenes* infections are becoming more frequent and probably more virulent. It is their feeling that the increased incidence and pathogenicity are due to the fact that chemotherapeutic measures have eliminated susceptible organisms, giving the resistant strains a clear field. Felty and Keefer²² reported the urinary tract to be the portal of entry in 16 of 28 cases of blood stream infections with the *Escherichia-Aerobacter* group. They also observed that the colon bacillus does not tend to invade the blood stream spontaneously, but usually follows cystoscopy or surgical trauma. This happened in 20 of their 28 cases. When sepsis occurs, the local lesion is usually extensive.

Libman³ has stated that "acute bacterial endocarditis arises secondarily to active purulent foci." In his experience, the colon bacillus enters the blood by

way of the genitourinary tract, uterus or gall-bladder. The bacteremia or pyelonephritis due to *Bacterium coli* follows genitourinary manipulation.

Keefer,²³ in reporting on the pathogenesis of bacterial endocarditis, has shown from studies in man and experimental animals that certain factors are usually present. They are (1) previously damaged or injured heart valve, (2) presence of platelet thrombi on the surface of the heart valve, (3) bacteremia, and (4) the presence of antibodies which aid in sterilizing the blood and in the focalizing of bacteria. He and others have shown that bacterial endocarditis in man most commonly develops on previously damaged heart valves as the result of rheumatic fever or congenital heart disease. This is especially true when the disease is caused by nonhemolytic streptococci or organisms of low virulence. In striking contrast are the cases in which the bacteria are implanted on normal heart valves, for in these the infection is likely to be caused by much more virulent organisms and the disease to be much more acute. In discussing the mechanisms by which bacteria invade the heart valves, Keefer points out two possibilities. They are (1) surface invasion, and (2) bacterial emboli to the heart valve. Inasmuch as there are many heart valves found involved in bacterial endocarditis which have no vessels, he favors the theory of surface invasion. He also points out that studies of vegetations usually show bacteria on the surface. It has been shown by Grant, Wood and Jones²⁴ that deformed or injured valves are more likely to develop platelet thrombi. These platelet thrombi make peculiarly favorable areas for the localization of bacteria. Since they are relatively free from leukocytes, bacteria which localize here are better able to survive. The mechanism by which bacterial vegetations develop on normal heart valves is not quite clear. Keefer is of the opinion that immunologic factors play an important rôle. Bacterial endocarditis has been produced experimentally in animals with normal heart valves. Wright²⁵ has shown that it is more likely to occur in rabbits which have been previously treated with vaccines to the point of developing demonstrable antibodies. Wadsworth²⁶ has also reported that when pneumococci were used with horses, bacterial invasion of the heart valve occurred only after the antibody titer of the blood became high. Experimental endocarditis may correspond closely to bacterial endocarditis in man without previously damaged heart valves, in that it follows bacteremia and the development of antibodies.

Although Herrell and Heilman²⁷ in 1947 listed *Aerobacter aerogenes* and *Escherichia coli* as being highly sensitive to streptomycin, other reports vary in the number of naturally resistant strains. Some bacteria may develop resistance to streptomycin with incredible rapidity. Future chemotherapy depends on the discovery and development of new and better chemotherapeutic agents.

The following is the report of a fatal case of bacterial endocarditis caused by *Aerobacter aerogenes*.

CASE REPORT

The patient was a 22 year old white housewife. There was no history or evidence of preëxisting heart disease or valvular lesion. She had had some difficulty with a "spastic colon" but was otherwise in good health.

This patient had delivered a normal child on October 6, 1947. Her pregnancy and delivery were uneventful with the exception of an infection of the urinary bladder with a nonhemolytic *Staphylococcus aureus* in the eighth month of pregnancy. This responded promptly to sulfathiazole. She was examined on January 8, 1948, at which

time she had no urinary symptoms, and the urine was free from evidence of infection on a routine noncatheterized specimen. A culture was not done.

On March 4, 1948, the patient was seized with a sudden severe pain in the left flank, radiating to the left groin and accompanied by urinary frequency and gross hematuria. She was hospitalized, and a plain film of the abdomen and an intravenous pyelogram showed what appeared to be a calculus in the lower part of the left ureter. She was afebrile, but in the urine there were numerous red blood cells. A urine culture was negative. The patient was discharged the following day with instructions to watch for the passage of a stone. She remained home for a week, during which time she was afebrile but experienced considerable colicky pain in the left flank.

On March 12, 1948, she was readmitted to the hospital for further study. A plain film of the abdomen showed again the same shadow, which was interpreted as being a ureteral calculus. Inasmuch as she had made no progress with the stone and was in considerable discomfort, it was felt advisable by the attending urologist to do a cysto-



FIG. 1. Left kidney, removed at operation, showing multiple abscesses on the surface from which *Aerobacter aerogenes* was cultured.

scopic examination. This was done on the day of admission, along with a meatotomy of the ureteral vesical orifice on the left. The right ureter was not catheterized. A catheter was left in the left ureter, but it was withdrawn after six hours because it caused the patient extreme distress. Studies of the roentgenograms obtained by means of retrograde pyelography revealed the shadow, which had been considered a calculus, to be about 1 mm. outside of the ureter, and probably a phlebolith. Culture of the urine taken at cystoscopy was reported positive for a coliform organism, later identified as *Aerobacter aerogenes*.

Following cystoscopy, the patient's temperature rose steadily, so that by the morning of the next day it was 103.4° F. It returned to normal at noon and then again rose rapidly to 105.6° F. During this time the patient was experiencing considerable pain and discomfort in the left flank and also had several severe chills. Penicillin was started in dosage of 1 million units each 24 hours. The temperature subsided the next day (March 14) and was normal by 4 p.m. At this time the patient had another chill

and the temperature again rose to 103.4° F. On this day the laboratory reported that the urine culture contained *Aerobacter aerogenes*. In view of the failure of penicillin to control the infection, streptomycin, 300 mg. every three hours, was added. The temperature again dropped on March 15, only to rise again the same evening to 102.8° F. During this time the pain and tenderness in the left flank in the area of the costo-vertebral angle had persisted. There was persistent pyuria. A blood culture taken on March 12 was reported positive for *Aerobacter aerogenes*, four colonies per c.c. A diagnosis of acute pyelonephritis was made. She was treated with penicillin, streptomycin and intravenous sulfadiazine and sulfathiazole.



Fig. 2. Left kidney, removed at operation, sectioned, showing multiple abscesses and areas of hemorrhage.

She showed evidence of a septic state for the next two days. A spiking temperature, chills, pain in the left loin and tenderness and pyuria continued. There was also tenderness in the right costovertebral angle. The organism recovered from the blood culture was reported highly resistant to both penicillin and streptomycin in vitro. On March 18 she was seen by another urologist, who agreed with the diagnosis of pyelonephritis. He suggested that the left kidney pelvis be catheterized again and that, if no improvement followed, the left kidney be explored. The kidney pelvis was catheterized and no improvement resulted. On March 19 the left kidney was exposed, its surface was seen to be grossly nodular, and multiple small abscesses were noted (figures 1 and 2). Left nephrectomy was carried out uneventfully.

Microscopically, the kidney showed an extensive inflammatory reaction with infiltration of numerous lymphocytes and plasma cells and, in some areas, a heavy exudate of polymorphonuclear leukocytes. There was actual liquefaction of the tissues in some areas, with formation of suppurative foci. The pathologic diagnosis was chronic and acute suppurative pyelonephritis. The ureter was free from infection. There was no pyoureter or pyelonephrosis.

Following nephrectomy, the patient began to improve rather slowly. A blood culture taken the day after operation was negative, as were subsequent ones taken during this hospital stay. The temperature subsided slowly and was normal on the sixth postoperative day. She began to eat well and was up and about her room.

On March 22 (the third postoperative day), a systolic murmur was noted over the mitral area. This had not been heard before by any of the several physicians who had had occasion to examine her. The possibility of bacterial endocarditis was consid-



FIG. 3. Mitral valve with bacterial vegetation on the papillary muscle. Sectioned area contained a bacterial vegetation shown in figure 4.

ered at this time. Repeated blood cultures, however, were reported negative. Following a normal temperature for five days, it was decided to allow the patient to go home, where it was felt she would be more comfortable and would take more nourishment. It was planned to follow her urine and blood cultures at short intervals.

She was fairly well for a week and then again became ill. Her temperature was elevated, and she had repeated mild chills. It was noted at this time that the mitral systolic murmur was higher pitched and harsher than on previous examinations. She also complained of pain and discomfort in the left lower abdomen and nausea and vomiting.

She was re-admitted to the hospital. The hemoglobin was 14.5 gm. and the red blood cell count was 4,260,000. The white blood cell count was 8,950, with 85 per cent polymorphonuclears. The urine contained numerous pus cells and *Aerobacter aerogenes*. The non-protein-nitrogen was 35.2 mg. An outstanding feature of the illness

on this admission was the persistent nausea and vomiting, which were not relieved by Wangensteen's suction. This was accompanied by a septic type of temperature, and again the blood culture was reported positive for *Aerobacter aerogenes*.

A report from the laboratories of Merck & Co., where the organism had been sent for sensitivity tests, revealed it to be highly resistant to penicillin and streptomycin and also to Bacitracin 100 u./c.c., Subtilin 1000 u./c.c., and Greisenin 100 u./c.c.

Inasmuch as the organism was not sensitive to any known chemotherapeutic agent, it was decided to try a bacteriophage. A stock phage was used to begin with, and was followed by a specific phage on April 20. At first the bacteriophage appeared to be

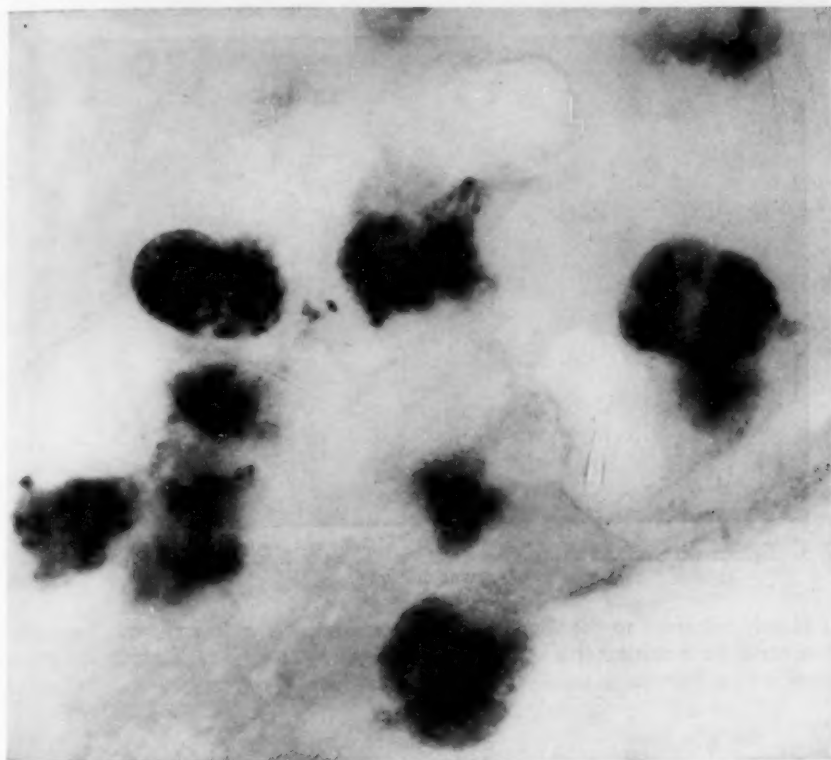


Fig. 4. High power photo of bacterial vegetation from the mitral valve containing gram-negative rods. On culture these were proved to be *Aerobacter aerogenes*.

helpful, but the slight improvement did not last and more organisms appeared in the blood stream. Up to this point, the specific phage was the only substance found which would lyse the organism.

Polymyxin was obtained and administered for the last two days of her life. The preparation used was polymyxin C, lot B-71, and was impure. The patient apparently took the drug well, showing no effect on kidney function, and there seemed to be a remarkable drop in her temperature following its administration. The organism was reported later to be very sensitive to polymyxin. The improvement, however, was transient and the patient died on April 23, 48 hours after the drug was started. The immediate cause of death was acute myocardial failure, which had been increasingly

evident for several days preceding death. It is interesting to note that while on polymyxin, the number of organisms reported in the blood culture dropped from 64 col./c.c. to 1 col./c.c. in the first 24 hours, then again rose to 28 col./c.c. on the last day.

At no time during the last hospital admission was her spleen palpable. There were no petechiae present until the third day before death, when they were noted on both conjunctivae. Urinary output remained good throughout the illness.

The outstanding findings at autopsy were bacterial vegetations on the otherwise normal mitral valve (figure 3). *Aerobacter aerogenes* was cultured from the vegetations, and they were also noted to contain gram-negative rods (figure 4). A large infarct of the spleen which measured 8 cm. across was also noted (figure 5). The spleen

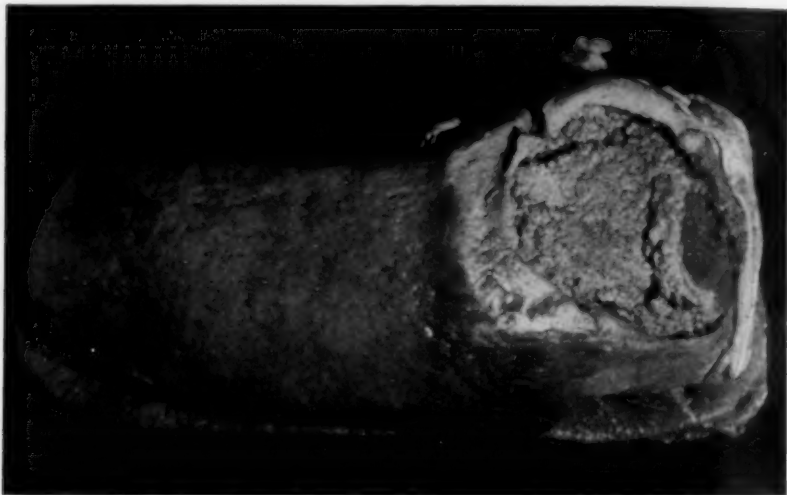


FIG. 5. Spleen with infarct measuring 8 cm. in diameter from which *Aerobacter aerogenes* was cultured.

was closely adherent to the diaphragm and stomach. The heart showed moderately severe acute toxic myocarditis. The right kidney was enlarged, weighing 270 gm., and showed mild diffuse interstitial inflammation and tubular degeneration.

DISCUSSION

A number of points mentioned previously in this report are illustrated by this case. Infection, although present in the genitourinary tract, apparently failed to invade the blood stream until after cystoscopic examination and meatotomy. This has been stressed by Libman,³ Keefer²² and others in the production of blood stream infections by the *Escherichia-Aerobacter* group. That *Aerobacter aerogenes* can cause bacterial endocarditis has also been demonstrated.

When dealing with chemotherapeutic-resistant organisms in the treatment of bacterial endocarditis, one is impressed by the futility of measures other than chemotherapy. Unfortunately, in this case polymyxin was not used early enough to give it a fair therapeutic trial. Had myocardial failure not intervened, it seems logical to expect that the patient might well have responded, as have others, to the proper chemotherapeutic agent. Certainly, the drop in the number of bacteria reported in the blood culture is striking.

When faced with laboratory evidence of high resistance of the causative organism, the treatment of bacterial endocarditis presents many difficult problems. One is hard pressed to decide whether to continue chemotherapy. Buggs, Hirshfeld²⁸ and associates have reported variations in the in vitro and in vivo sensitivity of organisms. They also point out that it is difficult at times to determine whether the same organism is being isolated at different times from a given patient. They state that, from a clinical standpoint, it is important to remember that organisms which can easily be made resistant to streptomycin in vitro may at times retain their sensitivity in a patient, even though the patient has received repeated courses of chemotherapy. In view of these findings it would seem that, in a case such as the one presented, there was very little else to do than to continue chemotherapy, provided it did not harm the patient.

The importance of adequate laboratory facilities and methods of testing sensitivity of bacteria should again be stressed. Because of the development of resistance, it is important that all of the bacteria be eradicated as completely as possible. It has been shown by Klein²⁹ that resistant strains may develop from insufficient chemotherapy. A few resistant mutants may be left a clear field and may take the place of less resistant organisms. The importance of reevaluating the sensitivity of organisms is also again stressed, particularly when the infection fails to be controlled. All of these rules in the treatment of bacterial endocarditis have been emphasized many times before.

CONCLUSIONS

A fatal case of bacterial endocarditis, with associated urinary tract infection caused by *Aerobacter aerogenes*, has been reported. A brief review of the literature as to case reports, pathogenesis and treatment is included.

The author wishes to express appreciation to Merck & Co. and to Dr. Frank Meleny and Dr. Perrin Long for the assistance received in the treatment of this case.

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PERIARTERITIS NODOSA AND MULTIPLE MYELOMA: REPORT OF SIMULTANEOUS OCCURRENCE IN A PATIENT RECEIVING STILBAMIDINE *

By WILLIAM R. BEST, M.D., and GERALD FINE, M.D., *Chicago, Illinois*

It is the purpose of this communication to record the occurrence of periarteritis nodosa in a patient suffering from multiple myeloma and treated with stilbamidine.† To our knowledge, there has been no previously reported case having both of these diseases.

CASE REPORT

A 53 year old Negro mail carrier was admitted to the hospital complaining of pain in the extremities, weakness, increased perspiration and loss of weight during the previ-

* Received for publication June 4, 1949.

From the Departments of Internal Medicine and Pathology, University of Illinois College of Medicine, Chicago.

Aided by a grant from the Hematology Research Foundation, Chicago.

† 4,4-diamidinostilbene; furnished through courtesy of Merck & Co., Inc., Rahway, New Jersey.

ous six-month period. The onset of pain was gradual and was noted first in the calves, from which it spread to involve the shoulders, arms and neck. The pain was often nocturnal, was usually dull and aching in character but was occasionally sharp and shooting. The gradual and progressive weakness was accompanied by loss of appetite, loss of weight and increased sweating. The weight loss amounted to 43 pounds in six months. For several months the patient had taken daily doses of Anacin to relieve pain. During a brief period before admission he complained of epistaxis of increasing severity.

Four and one-half years before the onset of symptoms the patient had received treatment for gonorrhea, and on several occasions he had received sulfonamides for pneumonia. The last such episode was one year before onset of present symptoms. Family and other past history was noncontributory.

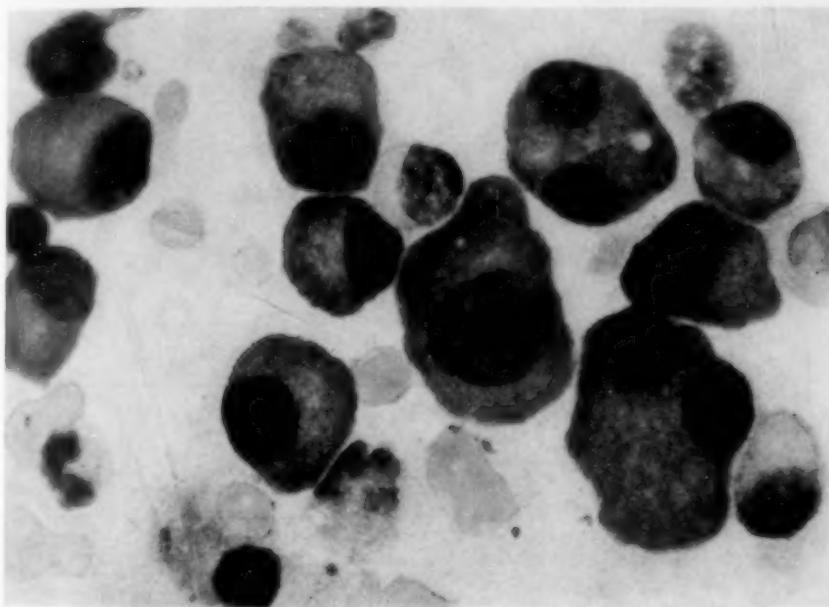


FIG. 1. Smear of sternal marrow showing infiltration with plasma cell type myeloma cells. Note immature, reticular form in center and smaller, more mature forms in periphery. There are two binucleate myeloma cells. $\times 1,000$.

Physical examination revealed a fairly well developed but pale and moderately wasted light-colored Negro man. Temperature, pulse and respirations were normal. Blood pressure was 160 mm. Hg systolic, 100 mm. diastolic. The liver was palpable two fingerbreadths below the costal margin. There was moderate weakness of the lower extremities, marked bilateral tenderness of the calf and arm muscles, and absent cremasteric reflex on the right.

Laboratory Procedures: There was a severe anemia. Red blood cell count was 2,300,000; hemoglobin, 5.5 gm.; hematocrit, 21 per cent; reticulocytes, 3 per cent; corrected Wintrobe sedimentation rate, 20 mm. per hour. On differential count there were 1 per cent neutrophilic metamyelocytes, 16 per cent neutrophilic staff cells, 54 per cent polymorphonuclear neutrophils, 2 per cent eosinophils, 22 per cent lymphocytes, 5 per cent monocytes with rare myelocytes and normoblasts. Toxic granulation of neutrophils was 3 to 4 plus, and red blood cells exhibited slight anisocytosis, poikilocytosis and

hypochromia. Sternal aspiration revealed 30 per cent typical myeloma plasma cells (figure 1). Urinalysis, spinal puncture and gastric analysis were within normal limits. Bence-Jones proteinuria was not demonstrated on four separate urine examinations. Blood contained: albumin, 1.6 gm. per 100 c.c.; globulin, 7.7 gm.; non-protein-nitrogen, 32 mg.; urea nitrogen, 12.5 to 13.5 mg.; creatinine, 2.2 mg.; phosphorus, 3.3 mg. Urea clearance was 56.5 per cent of normal; phenolsulfonphthalein excretion was 5 per cent in first hour, 25 per cent in second hour. Range of specific gravity of urine was 1.006 to 1.016 on concentration-dilution test. Roentgenologic survey of skeletal system showed an expanding lesion of the fifth left rib, with smaller lesions in the third and fourth left and sixth right ribs. There were mottled areas of radiolucency in the pelvis, and questionable radiolucencies in the skull and proximal third of the right radius.

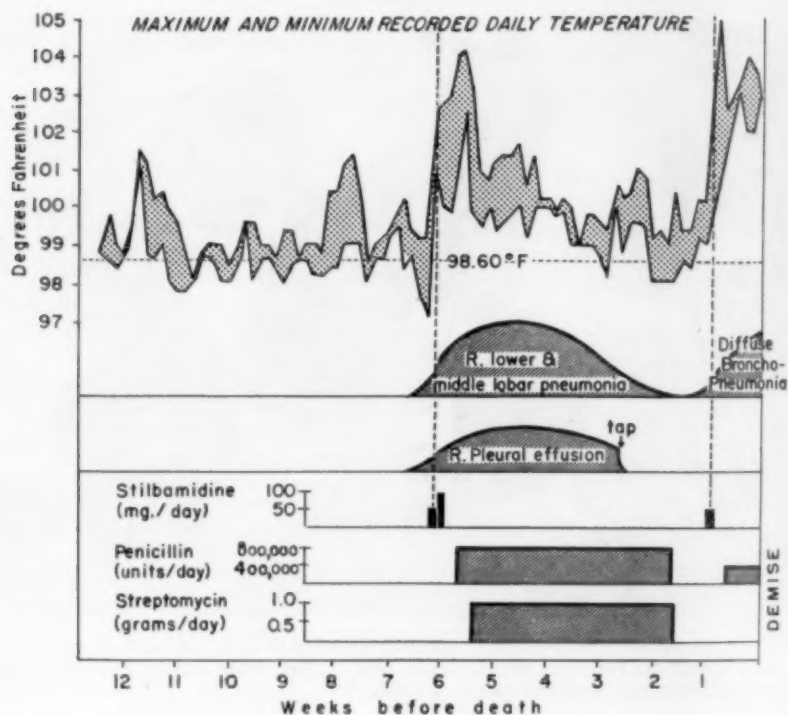


FIG. 2. Clinical course of patient while in the hospital.

Hospital Course (figure 2): After preliminary work-up, patient was placed on animal protein-poor diet and given 50 mg. stilbamidine intravenously. He experienced moderate diaphoresis and had a slight local reaction to the injection. His temperature began to rise on the day of this injection. The next day he was given 100 mg. of the drug. His temperature rose to 103° F. on that day. He experienced marked increase of malaise and had moderate thoracic pain. Diagnosis of lobar pneumonia with right pleural effusion was made by physical and roentgenologic examination. Stilbamidine was discontinued and his pneumonia was treated with penicillin, streptomycin and blood transfusions. Pleural aspiration was also done, and 200 c.c. of clear straw-colored fluid were removed.

One month later, after recovery from the pneumonia, he was given 50 mg. stilbamidine intravenously. There were no immediate reactions, but the temperature rose to 102° F. the same afternoon and to 105° F. the following afternoon. Stilbamidine therapy was again discontinued, and penicillin and blood transfusions were administered. His temperature remained elevated at about 103° F. but he had no specific complaints. He died quietly in his sleep six days after the second injection of stilbamidine. During his hospital stay, repeated blood and bone marrow studies, skeletal surveys, urinalyses and blood chemistry showed little change.

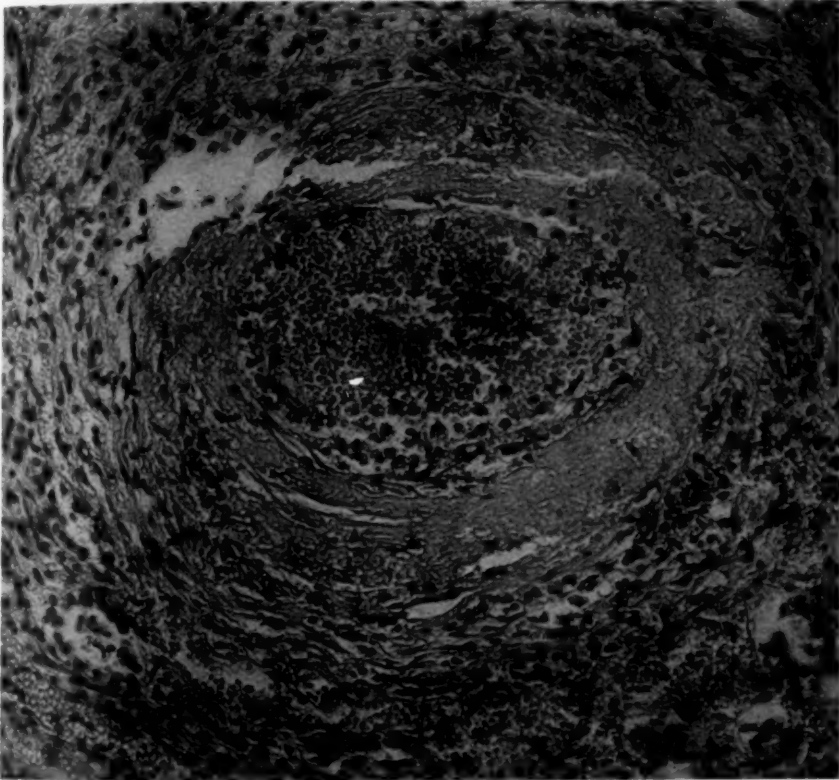


FIG. 3. Section of kidney showing an early lesion of a small muscular artery. There is marked necrosis of the vessel wall with minimal perivascular inflammatory exudate. Red blood cell debris is seen in the lumen. $\times 150$.

Pertinent Autopsy Findings: Gross examination revealed (1) myelomatous involvement of the left fourth and fifth ribs, with involvement and fracture of the right sixth rib; (2) large, pale, mottled kidneys, weighing 290 gm. (right) and 300 gm. (left); (3) bilateral diffuse bronchopneumonia; (4) large, mottled liver weighing 2,400 gm.; and (5) minimal bilateral pleural effusion with friable pleural adhesions on the right.

Microscopic study showed infiltration of the bone marrow with myeloma plasma cells. In addition there were many necrotizing arterial lesions in various organs. The kidneys were most severely involved, but organs affected to a lesser extent included



FIG. 4. Section of kidney illustrating early lesions in several arteries. Note predilection of lesion for bifurcation of arteries. Lesions are at an early stage, manifesting fibrinoid necrosis of the vessel wall and perivascular inflammatory exudate. $\times 35$.



FIG. 5. Section of kidney illustrating late stage of process near a bifurcation. There is considerable fibrosis of subintimal layers, with marked narrowing of the lumen. Some inflammatory cells are seen to right. $\times 100$.



Fig. 6. Section of kidney showing late stage of arterial lesion. There is marked fibrosis with narrowing of the lumen. $\times 80$.

the heart, liver, pancreas, intestinal tract, thyroid, testes and prostate. No lesions were seen in the sections of lung and spleen. These lesions involved mainly the medium and large arteries, and varied from acute to chronic or healed stages. The most acute lesions exhibited fibrinoid degeneration of the vessel wall, with extensive vascular and perivascular infiltration of neutrophils, eosinophils and lymphocytes (figures 3, 4). The older lesions showed fibrosis of the entire vessel wall and, in some instances, obliteration of the lumen (figures 5, 6). At several places lesions were observed to appear near the bifurcations of vessels (figures 4, 5). The kidney also showed mild tubular degeneration and, in a few glomeruli, fibrinoid degeneration involving the basement membrane of the intercapillary glomerular tufts and Bowman's capsule. There was associated inflammatory cellular infiltration.

Sections of lung revealed bronchopneumonia.

The cause of death was believed to be bronchopneumonia superimposed on the general debility of his underlying diseases. However, the fact that the patient received therapy with stilbamidine requires consideration of a possible toxic or hypersensitive reaction.

DISCUSSION

Recently there have been two promising lines of investigation into the etiology of disseminated, necrotizing arterial lesions. Rich and others¹ have demonstrated that such arterial changes in man and rabbits may represent manifestations of hypersensitivity to serum, sulfonamides and other drugs.

Selye and others² have produced periarteritis-nodosa-like lesions in rats by controlled injury to the kidneys, followed by an increase of the circulating sodium ion and adrenal cortical steroids.

Zeek, Smith and Weeter³ carefully studied the pathologic changes in rats injured by a variation of Selye's technic, as well as autopsy material from 31 cases of necrotizing panarteritis in man. On clinical and pathologic evidence they separated these human cases into two major types: (1) Those occurring as a reaction to drugs and exhibiting uniform, acute arterial lesions are termed "hypersensitivity angiitis." (2) The term "periarteritis nodosa" is applied to those disorders in which the arterial lesions resemble those induced by the kidney-adrenal experiments in rats. Drug sensitivity is not conspicuous in the histories of these patients. Most cases of necrotizing arteritis reported in the earlier literature and about half of those currently described would appear to fall into this latter group.

The typical arterial lesions of "periarteritis nodosa," according to these authors, start as a plaque of degeneration in the adventitial layer near a bifurcation of a muscular artery close to its entrance into an organ. This is followed by periarterial fibroblastic proliferation and infiltration with polymorphonuclear neutrophils, eosinophils and lymphocytes. The necrosis of the outer media spreads proximally, distally and circumferentially, as well as inward, to involve all layers of the arterial wall. Later, granulation and fibroblastic scarring occur in the necrotic area. Lesions in all stages of development are seen in most of the cases. The pulmonary arteries are practically never involved, nor are the splenic follicular arteries. Veins are affected only by extension from arterial plaques.

Hypersensitivity angiitis, on the other hand, involves the smaller arterioles and venules of all viscera, including the lung, and all lesions are of approximately the same age. The first change involves edema and degeneration of the intima and inner media. Later there is more extensive fibrinoid degeneration, with pleomorphic perivascular exudate. Fibrosis and healing are not seen as frequently or

in as great amount as in classical periarteritis nodosa. Usually the appearance of an individual arterial lesion is not sufficiently characteristic to warrant classification, and one must consider uniformity, distribution and morphology of lesions from many sites.

The vascular changes observed in the present case (table 1) fit most closely the criteria for "periarteritis nodosa" as described by these authors.

Assuming a possible allergic etiology, we should examine stilbamidine as a potential sensitizing agent. Both stilbamidine and the sulfonamides contain reactive amine groups closely associated with benzene rings (figure 7). The sulfonamides, which have been widely implicated in hypersensitivity angitis, when

TABLE I
Arterial Lesions of Reported Patient as Compared to Typical Vascular Pathology of
"Periarteritis Nodosa" and "Hypersensitivity Angitis"

Characteristics	Findings in Patient	Periarteritis Nodosa	Hypersensitivity Angitis
Organs affected	Kidney most marked; also liver, heart, pancreas	Kidney (80 per cent), heart (70 per cent), liver and other organs	Widespread—all organs may be affected
Organs <i>not</i> affected	Lungs, spleen	Pulmonary system, splenic follicular arteries	None
Type of arteries involved	Muscular arteries at bifurcations	Muscular arteries at bifurcations—near hilus	Small intrinsic arterioles
Veins	Not involved	Rarely by extension	May be primarily involved
Uniformity of lesions	All stages found	All stages found	Uniform age of lesions
Characteristics of lesions:			
Early	Unable to classify exactly	Edema and degeneration of adventitial collagen	Intimal and inner medial necrosis
Late	Fibrosis	Granulation—later fibrosis, occasionally calcification	Fibrosis less frequent
Occasionally associated findings	Glomerular lesion	Terminal urticaria and eosinophilia	Necrotizing glomerular nephritis

combined to form azoproteins have been found to be antigenic.⁴ Stilbamidine readily combines with nucleoproteins, forming potential sensitizing agents.⁵ To date, however, allergic reactions have not been noted with this drug.⁶ It is possible that the patient under discussion became sensitized by the first course of medication and reacted to the second course one month later. However, the healing stage of many arterial lesions would indicate that the vascular disease was in progress prior to the second dose of the drug. The doses of stilbamidine given were much too small to result in a direct toxic effect.

Table 2 reviews the principal clinical findings of the patient as compared to the incidence of similar findings in reported series of periarteritis nodosa⁷ and multiple myeloma.⁸ The nocturnal pain and tenderness in the extremities, which had

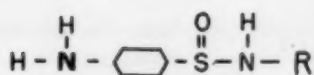
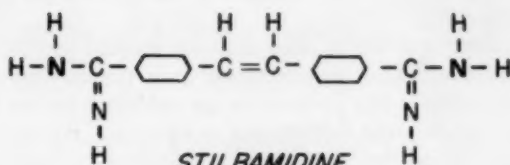
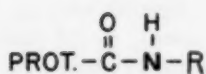
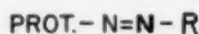
SULFONAMIDESSTILBAMIDINEPEPTIDE LINKAGEDIAZO LINKAGE

FIG. 7. Structural formulae of stilbamidine (4,4-diamidinostilbene) and the sulfonamides (p-amino-benzenesulfonamide compounds). Note that both of these drugs contain amino groups closely linked to benzene rings. Mechanism by which these compounds may combine with body proteins is also illustrated.

been present for nine months ante mortem, are definitely of a polyneuritis type. Polyneuritis has been noted in 45 per cent of reported cases of periarteritis nodosa, but it has not been mentioned in multiple myeloma. Increased sweating, which

TABLE II

Clinical Findings of Reported Patient Compared with Incidence of Similar Findings in Reported Series of Periarteritis Nodosa* and Multiple Myeloma†

Findings in Patient	Duration Prior to Death	Incidence in Reported Cases of:	
		Periarteritis Nodosa	Multiple Myeloma
Total illness	9 mos.	1-4 mos. in 50 per cent 1 wk.-4 yrs. extremes	1 mo.-5 yrs. 21 mos. average
Pain in extremities (nocturnal)	9 mos.	45 per cent have polyneuritis (pain in extremities)	86 per cent have pain but it is usually thoracic or lumbar and is relieved on retiring
Bilateral calf tenderness	Over 3 mos.	45 per cent polyneuritis	Not noteworthy
Increased sweating	9 mos.	Common with polyneuritis	Not noteworthy
Weight loss (42 lbs.)	9 mos.	44 per cent	Common
Anorexia	9 mos.	33 per cent	Not noteworthy
Epistaxis	3½ mos.	Not noteworthy	7 per cent (associated with hyperglobulinemia)

* See reference 7.

† See reference 8.

was also present for nine months, has been characteristically found along with the polyneuritis of periarteritis nodosa. Weakness, loss of weight and anemia are common to both conditions. Multiple myeloma was demonstrated at the time of admission three months before death. Epistaxis, which is roughly correlated with level of plasma globulin in myelomatosis, was present for only a brief period before hospital admission.

From this comparison it would seem that the clinical picture dating back nine months from death could best be explained as a manifestation of periarteritis nodosa. Multiple myeloma was present for an unknown period but probably was not responsible for the original debilitating symptoms. At autopsy the myelomatous lesions were of a degree suggesting a contributory rather than a primary cause of death.

This analysis of long-standing symptoms, together with the histologic pattern of classical periarteritis nodosa (fibrosing lesions), would make one believe that arterial lesions were present long before the patient first received stilbamidine. On the other hand, the sequence of events immediately preceding death does cast suspicion on this agent. It is possible that stilbamidine may have induced an acute exacerbation of the periarteritis, but we are of the opinion that, in this patient, multiple myeloma and periarteritis nodosa occurred simultaneously on the basis of chance alone.

SUMMARY

The clinical history and autopsy findings of a patient exhibiting both multiple myeloma and periarteritis nodosa are described. Possible relationship of these two conditions to each other and to treatment with stilbamidine is considered. It is concluded that the simultaneous occurrence of the two disorders is coincidental.

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BILATERAL CORTICAL NECROSIS OF THE KIDNEYS FOLLOWING TREATMENT OF AN UNUSUAL CASE OF HEART BLOCK *

By DAVID E. HAFT, M.D., and JOHN T. PRIOR, M.D., *Syracuse, New York*

BILATERAL necrosis of the renal cortex, which presents such a distinct clinical and striking pathologic picture, was first recognized by Juhel-Renoy¹ in 1886 in a young female with scarlet fever. Of the approximately 100 cases that have been reported to date, one-half have occurred in association with pregnancy, the rest in a variety of situations, including acute infections and alcoholism.² It is not within the scope of this paper to discuss the symptomatology, pathology and clinical course of bilateral cortical necrosis. These considerations have been excellently reviewed by Ash³ and more recently by Duff and More.²

A short time ago we had an unusual opportunity for study of a woman with partial heart block and Stokes-Adams seizures. At necropsy this patient demonstrated the classical picture of bilateral cortical necrosis of the kidneys. As it is our impression that part of the therapy employed may have been responsible for the renal lesion, we believe that a detailed report of this case will be of significant value.

CASE REPORT

A 54 year old female was admitted to the University Hospital on September 29, 1948, because of fainting spells.

Between 1929 and 1935 she had been admitted to the hospital several times, the usual presenting symptom being shortness of breath. During that period she was markedly obese, weighing about 270 pounds. The heart was not enlarged either by physical examination or by roentgenogram; the electrocardiogram was normal, and the blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. Because of a positive serologic test for syphilis, she was treated with arsenic and bismuth between 1932 and 1934; the serologic test later became negative. She was re-admitted on March 30, 1947, because of marked weakness and dyspnea following a fainting spell on the previous day. Examination disclosed a ventricular rate of 24 due to 5:1 heart block. Normal sinus rhythm returned spontaneously a few hours after admission, although there was a persisting right bundle branch block. Some time after discharge, bradycardia due to partial heart block returned permanently. For several months she received ephedrine, gr. $\frac{3}{8}$ three times a day, but during the month before the present admission her only medication was phenobarbital. Meanwhile she complained constantly of weakness. There

* Received for publication July 16, 1949.

From the Departments of Medicine and Pathology, Syracuse University College of Medicine, Syracuse, New York.

were numerous episodes of sudden faintness, especially in the last two weeks, and she had fallen to the floor unconscious on several occasions.

Physical Examination: The patient was an obese woman of large stature who was in no acute distress. The temperature and respirations were normal. The pulse was regular at 25; blood pressure was 170 mm. Hg systolic and 90 mm. diastolic. Slight enlargement of the thyroid was noted. Râles were heard in the left lung base. The left border of cardiac dullness was 1 cm. to the left of the midclavicular line; a rough grade two systolic murmur was heard all over the precordium, loudest at the aortic area. Auricular contractions could be heard faintly in diastole. The liver and spleen were not palpable. There was no peripheral edema.

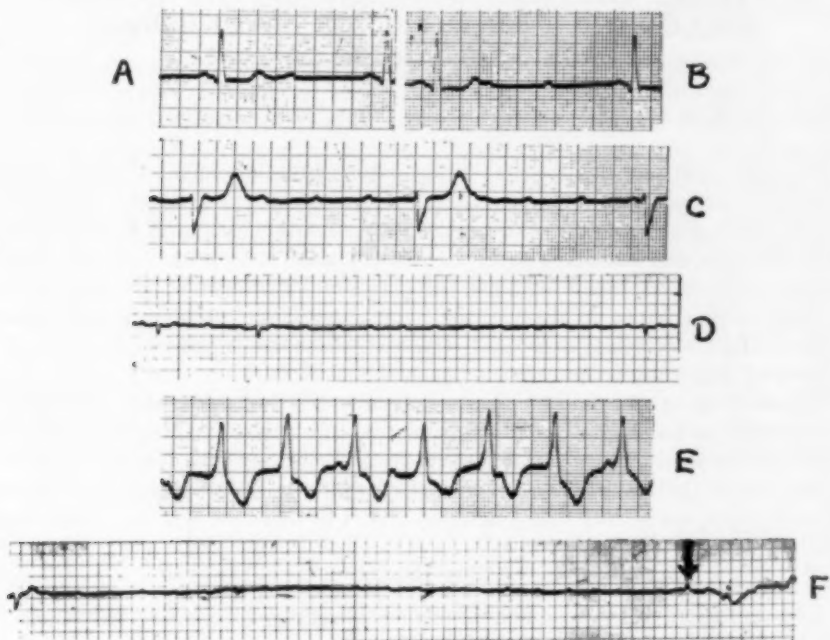


FIG. 1. Electrocardiographic tracings.

A. Lead I. Before intravenous injection of atropine, 1.8 mg. (auricular rate 70, ventricular rate 35). B. One minute after injection: auricular rate 85, ventricular rate 28. C. Lead II, showing complete heart block following first prolonged asystole on 10-6-48. D. Three hours before death, showing prolonged asystole due to partial block. E. Idiopathic ventricular rhythm with A-V dissociation (auricular rate 100, ventricular rate 85) after administration of barium chloride. F. Effect of needle puncture. At the moment indicated by the arrow, a needle was thrust into the heart chamber.

Laboratory Data: Complete blood count and urinalysis were normal. Urine culture was negative. Non-protein-nitrogen was 35 mg. per cent. The complement fixation test for syphilis was negative. Venous pressure was 125 mm., not rising on right upper quadrant pressure; circulation time with procholol was 30 and 35 seconds in separate injections. Roentgenographic studies of the chest showed pulmonary vascular engorgement and borderline cardiac enlargement. An electrocardiogram showed 2:1 heart block with ventricular rate of 32; in addition, the QRS was prolonged to 0.12 second, and precordial leads demonstrated right bundle branch block as in the previous admission.

Course in Hospital: It was demonstrated by the direct-writing Cardiette that intravenous atropine (1.8 mg.) caused the auricular rate to increase from 70 to 85, but failed to increase the ventricular rate because of concomitant change from a 2:1 to a 3:1 block (figures 1a and 1b). Epinephrine 0.5 mg. subcutaneously produced no significant changes. Exercise (20 step-ups) caused the auricles to accelerate to 105, but again there was an increase in the degree of block so that the ventricular rate did not exceed 40.

Because of evidence for some degree of heart failure, digitalization was attempted. Accordingly, on October 5, 1948, she received two doses of digitoxin orally, 0.6 mg. at 1:15 p.m. and 0.6 mg. at 7 p.m. On the following morning, 12 hours after the last dose, she complained of waves of faintness as experienced previously. These were found to

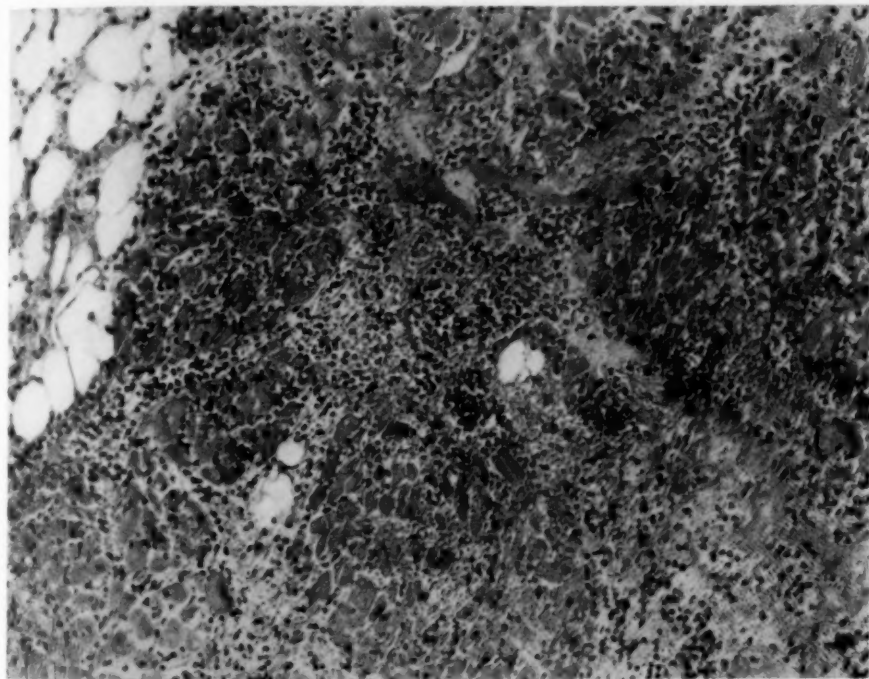


FIG. 2. Acute inflammatory cells throughout the interstitial tissue with preservation of the myocardial fibers. Patchy areas of adipose tissue can be seen. Hematoxylin and eosin stain, $\times 140$.

coincide with periods of asystole lasting up to five seconds. Finally, there was a prolonged asystole during which she lost consciousness, became cyanotic and gradually developed stertorous and then infrequent gasping respirations. An injection of 1.0 mg. of epinephrine was made into the cavity of the heart just to the left of the sternum. Shortly afterwards her pulse returned, first at rate 60 and then at 32, where it remained. The total duration of asystole was estimated at between five and 10 minutes; the precise interval was not observed in the excitement of the occasion. The electrocardiogram now for the first time showed complete heart block, with an auricular rate of 100 and ventricular rate of 33. During the next three hours she gradually regained consciousness but continued to appear very ill, with restlessness and moaning. Later in the day there were three more Stokes-Adams seizures, each due to asystole and

halted by intracardiac epinephrine. There follows a tabulation of drugs given between the first major asystole on October 6 and death on October 9:

Ephedrine, 50 mg. q3h subcutaneously \times 9, followed by 25 mg. q3h \times 9 (total, 675 mg. for three days).

Atropine subcutaneously, q3h: 1.0 mg. \times 3, then 1.2 mg. \times 3, then 0.4 mg. \times 3 (total, 7.8 mg. in one day).

Epinephrine, 1:1,000, four intracardiac injections on October 6:

1 mg. at 8:15 a.m.

2 mg. at 1:45 p.m.

1 mg. at 2:00 p.m.

1 mg. at 10:30 p.m.

Epinephrine dissolved in 10 per cent glucose infusion, 1.2 mg. in 36 hours.

Aminophylline dissolved in 10 per cent glucose infusion, 1.0 gm. in 20 hours.

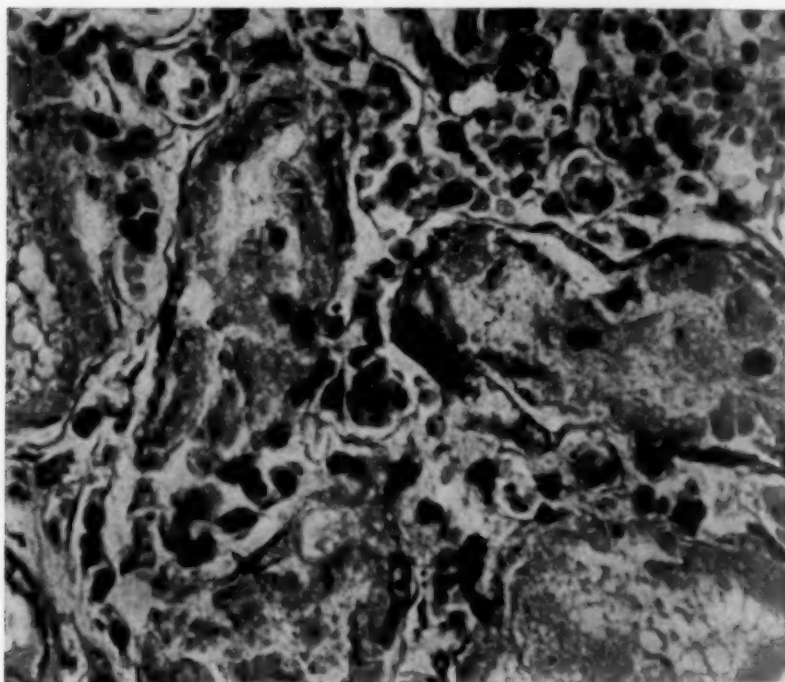


FIG. 3. Severe renal tubular necrosis throughout the section. A large dark regenerative nucleus is noted in the center of the illustration. Hematoxylin and eosin stain, \times 500.

No more digitalis was given. Between October 6 and 9 she remained in complete heart block, the ventricular rate varying between 24 and 40 (figure 1c). By the evening of October 6 her temperature had risen to 104.5° F. rectally; thereafter it did not drop below 102°. The blood pressure average was 110 mm. Hg systolic and 60 mm. diastolic. The patient remained restless and semiconscious. She voided 200 c.c. on October 7 and was incontinent of urine during the next night; during her last day an indwelling catheter failed to produce any urine. At 8:15 a.m. on October 9 she again became suddenly pulseless, cyanotic and comatose. This episode, like the others, was terminated by 1 mg. of epinephrine into the heart chamber. The electrocardiogram now

showed that complete heart block had been replaced by partial block with markedly prolonged ventricular pauses (figure 1d). Temporary improvement in ventricular irritability occurred after an intramuscular injection of 30 mg. of barium chloride at 8:30 a.m. (figure 1e). Prolonged asystoles started again at 11:30 a.m.; it was observed that the pulse could be restored temporarily at least by direct needle puncture through the myocardium, without epinephrine or any other drug (figure 1f). She died at noon on October 9. The non-protein-nitrogen was 104 mg. per cent four hours before death.

Gross Autopsy: The significant external findings were multiple needle puncture wounds over the anterior chest between the left third and fourth intercostal spaces, an area measuring 6 cm. in diameter. The pericardial cavity contained 200 c.c. of serosanguineous fluid, and the external surface of the pericardium revealed puncture marks

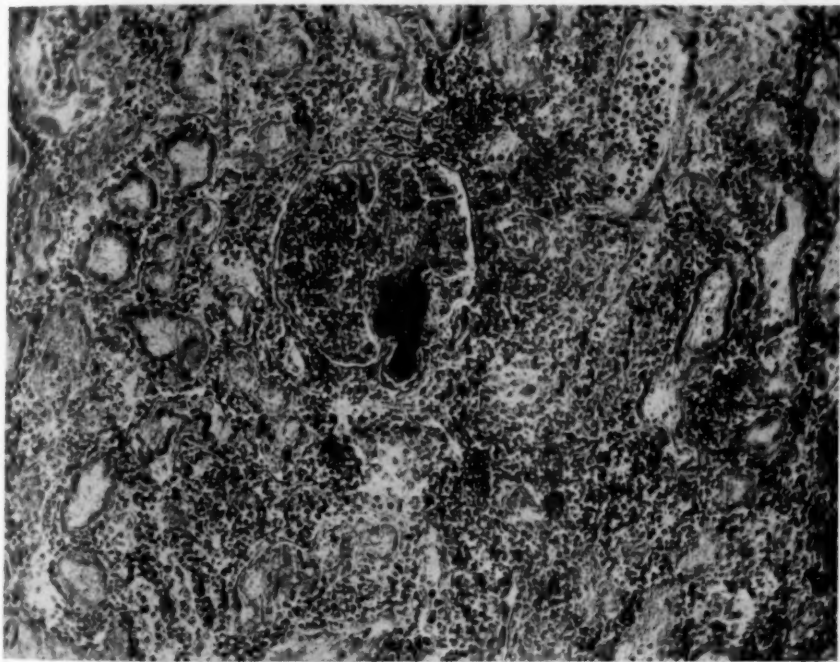


FIG. 4. A fibrin thrombus within an afferent arteriole extending into the glomerular capillaries. Masson-Goldner stain, $\times 140$.

corresponding to those described on the external body surface. The heart, weighing 550 gm., disclosed epicardial petechia-like spots on the anterior surface of both ventricles, these representing the needle puncture sites. On section these were seen to be hemorrhagic tracts extending through the endocardial surface. Slight right ventricular hypertrophy was noted. The liver weighed 2,000 gm. and on section presented the picture of marked congestion. Each kidney weighed 300 gm. and the capsules stripped with some difficulty, disclosing a reddish-brown external color. The cut surface was characterized by an over all reddish-brown color, but cortical and medullary markings were prominent. The other organs, including the brain, were grossly normal.

Microscopic Examination: Throughout the heart the interstitial tissue separating adjacent myocardial bundles appeared to have been replaced by large amounts of adipose tissue. Study of the needle tracts disclosed a well developed pancarditis in these

areas, characterized by large numbers of polymorphonuclear leukocytes (figure 2). An endocardial mural thrombus was seen at the termination of one such tract. The myocardial fibers were still well preserved, though some fibrinous exudate was noted on the epicardial surface. No bacterial colonies were recognized.

The kidneys presented the typical picture of cortical necrosis. This destructive process involved nearly the entire cortex, sparing only the subcapsular zone, the juxtamedullary cortex and rare small irregular areas within the cortex itself. The renal tubules and parenchyma in the involved areas were represented as ghostlike structures, the former maintaining their circular outline but being composed of smudgy eosinophilic anuclear material. Some tubules showed early attempted epithelial regeneration (figure 3). Stromal leukocytic infiltration and some hemorrhage were present. The necrotic glomeruli were generally congested, and many revealed fibrin thrombi within their capillaries. Similar thrombi were noted within the interlobular arteries and the afferent arterioles (figure 4). Study of the microscopic structure of the remainder of the organs, including the brain, disclosed only moderate pulmonary edema and some sinusoidal congestion and central necrosis within the liver.

DISCUSSION

Many hypotheses have been advanced in an effort to explain the pathogenesis of this atypical type of renal infarction. That the primary disturbance is circulatory is attested by the distribution of the lesion, which always spares the juxtamedullary and the narrow subcapsular layer of the cortex. The sequence of hypersensitivity of the cortical arteries and arterioles, resulting in stasis, thrombosis and subsequent necrosis of the renal cortex, has been accepted by the majority of authors. That there may be an associated redistribution of the intrarenal circulation was not made clear until very recently. Trueta and his collaborators,⁴ working largely with rabbits, have demonstrated a dual circulation to the kidney under the control of the autonomic nervous system. In the course of studying the effect of simulated crushing injuries to the hind limbs, they noted a prolonged reflex renal artery spasm in their animal. This phenomenon could be duplicated by stimulation of the afferent sciatic nerve fibers, efferent splanchnic nerve fibers, or by the administration of large doses of epinephrine, pitressin or staphylococcus toxin. By means of direct observation of the kidneys, radiographs and pigment injections, these workers have very clearly demonstrated the pathways involved in the redistribution of the renal circulation brought about by the above stimuli.

According to Trueta, conditions existing at the moment determine which of the two potential pathways the blood will course within the kidney. The cortical route passes from the interlobular arteries to the afferent arterioles, their glomeruli, efferent arterioles, the intertubular capillary network and into the interlobular veins. The shorter medullary shunt passes from the interlobular arteries very suddenly into large afferent arterioles, their juxtamedullary glomeruli, the vasa recta and into the interlobular veins. From the interlobular veins the two routes are identical, along larger venous trunks to the main renal vein.

Certainly the pathologic picture in bilateral renal cortical necrosis can be explained very adequately on the basis of interlobular artery constriction within the cortex, while the medulla, which remains viable, is supplied by the lesser circulatory route. The location of the fibrin thrombi described above under "microscopic examination" tends to support this view.

Some examples of the experimental production of bilateral renal cortical nec-

rosis are cited here because they emphasize the rôle of vasoconstricting substances, which presumably call into play the circulatory shunt described above. Penner and Bernheim,⁵ studying the production of shock in dogs, noted the lesion following the daily intraperitoneal injection of a 1:1000 solution of epinephrine hydrochloride. Byrom,⁶ working with rats, successfully produced cortical necrosis with large subcutaneous doses of pitressin. A very interesting hypothesis for the experimental production of the lesion is to be found in the work of Black-Schaffer, Hiebert and Kerby.⁷ These workers produced bilateral cortical necrosis by the injection of washed living meningococci into rabbits, and explained it on the basis of Schwartzman reaction, the Schwartzman substance presumably causing severe vasoconstriction of the interlobular arteries.

Human cortical necrosis has been reported in association with many substances which may be considered toxic to the individual. Epinephrine has not previously been implicated in the production of this lesion in humans. The case reported herein is complicated by circulatory stasis, and it is to be emphasized also that the synergistic action of the sympathomimetic agents, epinephrine and ephedrine, may have been further reinforced by the parasympathetic depressant, atropine. Although all these factors must be considered, we think it likely that the frequent intracardiac injections of large amounts of epinephrine played a contributory if not vital part in the pathogenesis of the renal lesion. The microscopic finding of renal tubular regeneration necessitates the lesion's being at least three days old; this corresponds rather well to the onset of prolonged asystoles and epinephrine overdosage. We cannot, of course, state with certainty that the cortical necrosis was the result of epinephrine, but there is a certain amount of evidence in the literature to support this view: (a) the experiments by Trueta⁴ and by Penner and Bernheim,⁵ which have shown epinephrine to be capable of causing, respectively, blanching of the renal cortex in rabbits, and the lesion of cortical necrosis in dogs; (b) the failure to demonstrate cortical necrosis resulting from circulatory arrest per se for a short interval (five to 10 minutes). Unfortunately, the information available on this last point is meager. Howkins et al.⁸ report the case of a young woman who survived 26 days after an episode of asystole of about 10 minutes; she remained in a decerebrate state and, at autopsy, showed profound destruction of the pyramidal cells of the cerebral cortex. However, the kidneys were only "congested and with cloudy swelling of the convoluted tubules." The patient we have described did not suffer this degree of cerebral injury, either clinically or pathologically; hence her asystole was probably shorter. Weinberger et al.⁹ did produce total circulatory arrest in cats for periods up to 10 minutes in order to observe the effects on the brain, but the kidneys were not studied. The fact that some animals survived indefinitely would militate against the occurrence of cortical necrosis. Scarff and Keele,¹⁰ after removing one kidney in the rabbit, produced total ischemia of the remaining kidney for periods of 60 to 120 minutes. There was a rise in the blood urea nitrogen to about 300 mg. per cent in all animals during the first few days, and, at autopsy, tubular necrosis of the proximal convoluted tubules with glomerular preservation was observed. Occlusion for as long as 120 minutes was not necessarily lethal, however. This experimental work has been reviewed to support our belief that heart block with its attendant circulatory arrest, for as short a period as 10 minutes, is probably not capable of producing renal cortical necrosis, per se.

Although irrelevant to the lesion under consideration, the effects of atropine, epinephrine and exercise on this patient are worthy of comment in view of the paucity of such observations in partial heart block. Atropine is sometimes effective in restoring normal A-V conduction¹¹; in such a case there must obviously be a vagal mechanism for the block. In complete heart block, atropine in large enough dosage will speed the ventricles as well as the auricles.¹² This is also true of epinephrine.¹³ In our patient it was apparent that there was a high degree of partial block on an organic rather than on a functional basis. This may have been the result of fatty infiltration, corresponding to the case report by Spain and Cathcart.¹⁴

Finally, we wish to emphasize that it was possible to restore ventricular systole temporarily, at least, by needle puncture alone, and that in desperate situations this may be preferable to the actual injection of epinephrine into the cardiac chambers. This procedure, however, may not be entirely without some risk, in view of the pancarditis developing along the path of the needle punctures, and the mural thrombus on the injured endocardial surface seen in this case. This therapeutic measure, frequently repeated, conceivably could give rise to difficulties of a most serious nature.

SUMMARY

An unusual case of complete heart block is described which, at autopsy, demonstrated the classical picture of bilateral renal cortical necrosis. Experimental work is reviewed in the light of the current concept of the pathogenesis of this condition. This study suggests that one of the therapeutic agents employed, i.e., epinephrine, may have played a vial rôle in the production of this atypical type of renal infarction.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. Richard H. Lyons, Professor of Medicine, for his valuable suggestions, and to Miss Stella Zimmer, of the Photography Department, for the photomicrographs and the reproduction of the electrocardiographic tracings illustrated here.

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A TWENTY-TWO YEAR FOLLOW-UP OF A CASE OF MUCOUS COLITIS *

By FRANKLIN G. EBAUGH, M.D., F.A.C.P., and JOHN M. LYON, M.D.,
Denver, Colorado

THIS is a report of a woman, now 53, who has had mucous colitis since 1926.

CASE REPORT

For the six years prior to 1926 the patient had gastrointestinal distress that occasioned an appendectomy, but it was in 1926, when she was seen by one of us (F. G. E.), that the diagnosis of mucous colitis was made. At that time she had many complaints; she said she was "all in." She suffered from back aches, insomnia, depression, fatigue, stomach trouble, and alternating constipation and diarrhea. She weighed 81 pounds but otherwise her physical examination was normal. Her past medical history was not remarkable. Since the age of 20, or 11 years prior to her admission to the Colorado Psychopathic Hospital, she had held one job, a responsible secretarial position in which she had demonstrated considerable ability. Personal history revealed that she was an only child and that her father had deserted the family when she was still an infant. She and her mother had always been extremely close, and they had never lived apart. She had had a few boy friends but no marriage proposals. There was no history of neurotic traits in childhood and she was said to have been a good, obedient child.

Verbatim reports from her history in 1926 include the following: "I always have a dread of being conspicuous in any way"; "I fear what people are thinking of me"; "I want to stay out of sight"; "I always shrink from any situation"; "I feel I must hang onto someone who cares"; "I fear not being well enough to take care of my mother when she is old"; "I fear being an old maid." She talked at length of her feelings of inferiority. She complained of inability to stand on her own feet or take her own part in any argument. She expressed her annoyance that she could never get angry or show resentment (expressed hostility). She was full of praise for her mother and expressed much tenderness for her.

* Received for publication May 30, 1949.

Presented at the Regional Meeting of the American College of Physicians, Denver, Colorado, March 1, 1949.

The patient stayed in the hospital for two months, during which time she was a model patient in every way. As her history unfolded, it became apparent that her main problem was one of emancipation from an over-loving, over-protective mother. She gained some understanding of this and recognized that at 31 she should be living her own life. She followed through with plans for moving away from her mother but she could never bring herself to the point of actually acknowledging all of her feelings. She left the hospital greatly improved, went back to her job and again was a successful worker.

In 1928, at the age of 33, she married. Her husband was a school teacher nine years her junior. The marriage was successful for the first few years and her health was no problem. Her weight went up to about 95. She had entered into the marriage with little interference from her mother, who was living in another city at the time. The mother, however, did not approve of the marriage and had continued to put pressure on the psychiatrist to allow her daughter to come back to her. The mother never accepted this separation and looked upon it as a cruel, unnecessary thing. In 1934 the mother suddenly lost her job and practically appeared on the patient's doorstep. There was nothing to do but take her in.

The patient's health history starts again in 1934. For a year or so she had slowly increasing gastrointestinal difficulty, for which she received medical attention. Her symptoms gradually got worse so that by 1937 she was back to about 80 pounds. She was having six to eight stools a day, with severe cramping and gas pains. In 1938 she was again seen (by F. G. E.), and she was found to be depressed, anxious and insecure. For a time she was diagnosed as having an amoebic dysentery, for which she was treated without results. Ultimately the story came out that her husband had become interested in another woman. This affair of the husband's was rather open and acknowledged. He had lost all interest in the patient and had moved into a separate bedroom. The "other woman" was the patient's best friend, and the affair seemed to produce no particular change in the friendship. The two women spent a lot of time together, openly discussing the husband's predicament, and yet apparently there was no outward show of resentment or anger on the part of the patient. In her trouble she leaned heavily on the woman who was taking her husband away from her. The three of them were together much of the time. The husband continued to have an indifferent air, but the friend adopted a very motherly attitude toward the patient, was sympathetic about her illness, helped her with her daily decisions, and in many ways was most patronizing. The patient had gradually slipped into the rôle of a sick child that two adults were caring for. She ceased to be a wife and actually made no protest that her rôle of wife had been usurped.

After a few weeks of psychiatric care she improved to a degree. The husband had accepted a lucrative teaching position in another city and the patient was determined to go with him. The move looked like a good solution to the triangle. She was doomed to disappointment, however, for in a few months the friend appeared on the same campus. The husband became even more indifferent and more open in his infidelity. The patient's symptoms became pronounced and she was forced again to seek medical care. An interesting sidelight is the fact that a clinician who cared for her diagnosed her as having Simmonds' disease and reported her case in the literature.

The next four years were very difficult. The husband changed positions two or three times. He became irritable, indecisive, and finally completely open in his desire to get a divorce and marry the other woman. In 1945, a divorce was obtained. The two women were living together at this time. The patient was humiliated but still showed no open resentment and did practically nothing to prevent the loss of her husband.

For the last three years she has been back in Denver. She has held a part-time job to supplement the alimony she receives. The husband married the other woman

and they now live in the East. The patient receives regular correspondence from the new wife and it is all very "chatty" and friendly. Each alimony check is accompanied by a nice note from the ex-husband. They still adopt a patronizing air toward the patient, worry about her health and finances, and send her advice. They are planning to visit her this summer.

Upon returning to Denver, the patient met with great sympathy from all her friends. They were attentive, considerate and helpful. Since she, the husband and his new wife had mutual friends, the situation was at times rather difficult. The patient wanted her friends to take her side, but since she never seemed resentful the friends were mystified as to her real attitude and kept quiet. As time went on many of the old friends began to be less attentive, and of course the patient no longer fitted into a married group. Her symptoms, which had lessened upon her return to Denver, began to reappear. She again sought medical advice, but her physical examination proved quite normal and she was referred once more for psychiatric attention.

Dr. Lyon first saw her the latter part of August, 1948. She was depressed, tearful and anxious, and expressed feelings of great loneliness and fear of the future. Her diarrhea was peculiar in that it occurred mostly in the mornings. Each morning prior to breakfast she would have six to eight loose, watery stools, each stool containing more and more mucus. She would force down a small breakfast and then determinedly set out for work. Through the rest of the day she would have but one or two movements, though she said she felt all through the day that she could have a bowel movement at any time. Evening found her exhausted but she could not sleep when she got to bed.

At this time she weighed about 108 pounds. She was a well dressed, extremely pleasant and intelligent woman who gave evidence of good cultural background. During the first few interviews she dwelt on her sorry plight, her fears of the future, her loneliness and her troublesome bowel symptoms. Much later it was ascertained that her mother had been in an old ladies' home here in Denver for the past eight years. She then began to relate the history of her marriage and told of her earlier medical treatment. From this point she went on to tell of her childhood experiences and her relationship with her mother. As she talked, she was able to identify her excessive passivity and her dependent attitudes. She quickly formed a dependent relationship with her doctor and began to have high expectations of a cure. When a cure did not materialize she was disappointed but could not show her disappointment. She admitted her resentment toward her physician only after it was pointed out to her. Slowly she found herself able to discuss her timid reactions and her fears of offending. Gradually she came to admit that underneath her meek exterior she felt hot resentment at the way life had treated her. She even came to the point one day of roundly denouncing this best friend who had stolen her husband. This outburst left her upset and ashamed. She cried when she told that for three years she had been carrying on a polite correspondence with her old friend when underneath she wanted to choke her. The uncovering of some of these hostile feelings was followed by an improvement of symptoms and also a change in her behavior. For example, her employer had been reducing her to tears several times a week by his critical remarks. One day, instead of bowing her head and taking his outbursts of ill temper, she lashed back at him and pointed out that he was unreasonable and mean. The next morning the boss left a present on her desk. She reported a dream in which she was walking down a street and an old friend gave her the cold shoulder. In the dream she turned back, caught up with this friend and "told her off" in no uncertain terms. She admitted that such behavior was what she longed to show but had never been able to. In real life she would have felt crushed, and would have gone home and cried because someone didn't like her. She expressed more and more feeling of resentment and anger. Finally she admitted these feelings toward her mother. She told how she

detested the weekly trips to the old ladies' home. She admitted that it was a relief when her mother didn't feel well enough to come to the apartment for Sunday afternoon, and yet she was resentful of her mother's illness because that caused inconveniences. At about this stage of treatment she went for over two weeks with no diarrhea, but the other symptoms, such as anxiety and insomnia, persisted. She herself felt she was much better and very obviously she was in a better frame of mind. She worked out for herself that she had grown up with a pronounced dependency on her mother which her mother had fostered. The loss of her father bound

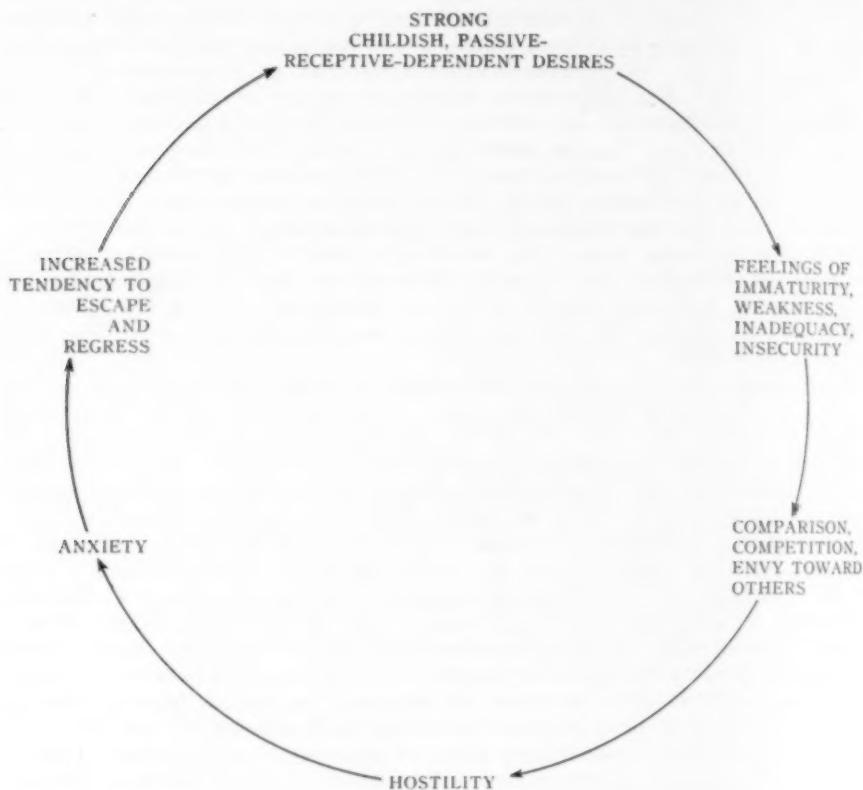


FIG. 1.

From Saul, L. G.: *Emotional Maturity*, 1947, J. B. Lippincott Company, Philadelphia, p. 75.

This diagram after Saul (figure 1) nicely pictures the emotional factors at play in the patient's illness.

the two women closely together, but the patient then recalled that as a child she had often wondered why her father had left her. She recalled small hints that had made her wonder if somehow she had driven him away. She had never known the truth, so now she went to her mother to find out what had happened. She learned that her father was a psychopath, a gambler, a totally irresponsible individual who had been very upset when he learned his wife was pregnant. The mother went on to recall the hardships she had experienced when she was left alone with an infant to raise. The patient began to understand her mother as never before. In her treatment ses-

sions she now recalled how, as a child, she had resented her mother's going to work and how she had hated being left with her grandmother and an idiotic uncle through the day. She also remembered that she had often wanted to be bad and to rebel but never had for fear she would lose her mother entirely. The vague idea that she had somehow been responsible for driving away her father undoubtedly played a rôle in her fear that her mother might go also. This accounted for her passive good behavior and laid the groundwork for her entire personality structure.

The talks with her mother allowed her to see that she had carried childhood resentments on into adult life, and her attitude changed to sympathy toward her mother and the resentments just about disappeared. She was able to see that her mother had had no easy time of it, and that what had appeared to her as rejection had been

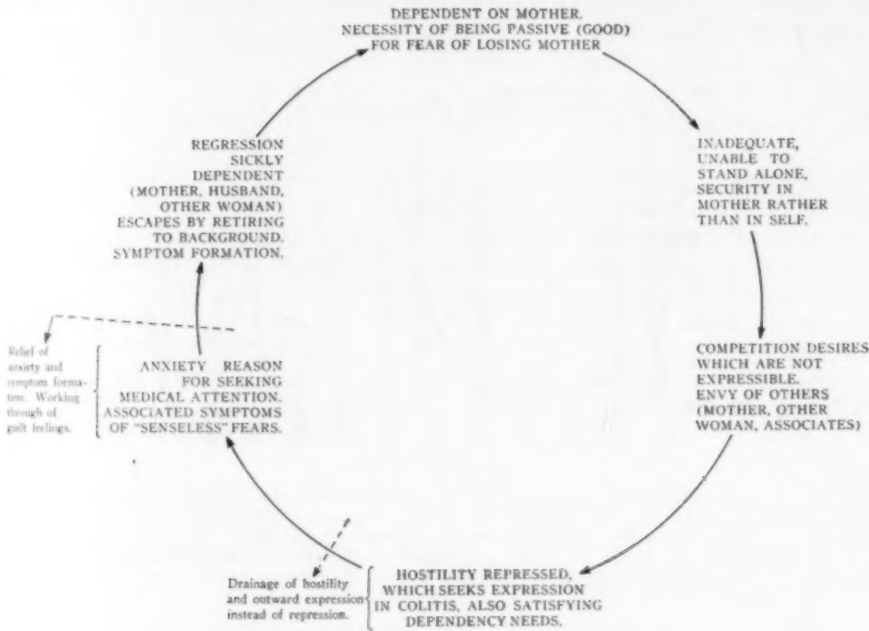


FIG. 2.

Figure 2 illustrates how the history and findings in this case can be superimposed on the above general formula, which is applicable to many such cases.

made necessary by reality. The grasping, smothering, protecting attitude the mother had later shown was, of course, a simple compensatory device that the patient could easily understand and forgive.

Shortly after this change in the patient's attitude the mother had a coronary thrombosis and for a few days was in critical condition. The patient's reaction was of course fairly dramatic: her diarrhea reappeared with the phone call from the home, but after two days she got control of her emotions and her behavior was most satisfactory. She expressed her gratitude that she had been able to relieve herself at least partially of her hostility toward her mother. She was acutely aware of the guilt feelings she would have had if her mother had died while she was still harboring feelings of resentment.

The history of this patient is rather interesting, but we have done little to explain why she has mucous colitis. A bit of theorizing is perhaps in order. We have three statements to make that are perfectly obvious, and in making them we stand the chance of losing whatever interest we have stimulated, but it is on these well known facts that we base our thinking and attempt to explain the etiology of this patient's colitis. First, it is well known that emotions can cause the autonomic system to respond. Different emotions produce different responses, and the gastrointestinal system, with its rich autonomic supply, is a good place to observe the rôle that psychic impulses play. We all know the peculiar abdominal sensation associated with fear. Many of use have had an annoying diarrhea under prolonged anxiety, and most of us have used a crude but rather accurate expression to describe lower bowel functioning under conditions of great and sudden stress.

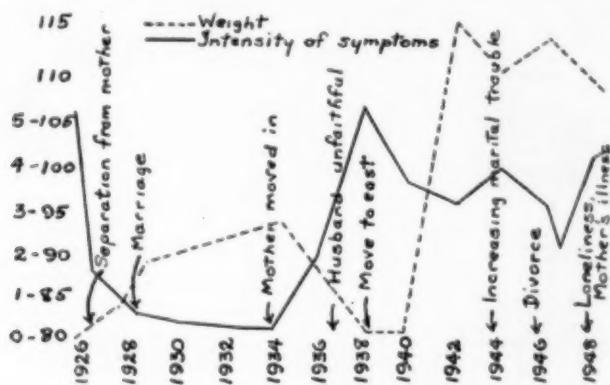


FIG. 3. The pathologic process is cyclic, and treatment is directed toward breaking this cycle. The dotted lines indicate one of the points of attack of the therapy, which in this case was directed toward the hostility and anxiety portions of the cycle. This approach successfully broke the chain of cyclic events and achieved at the same time a decrease in the insecurity and dependency feelings.

Second, "people are different." We will all admit that the obvious is more difficult to see than the unusual, and so it is in medicine. We have been so pre-occupied with disease that health, until recent years, has been taken for granted. That there are different levels of health has been such an apparent thing that description of normal behavior seemed no more than an elaboration of the obvious. However, normal people are different, and psychiatry is now interested in this fact. There are aggressive people, retiring people, independent people, dependent people, stubborn people and vacillating people. It is of interest in this connection to note that certain types of people have certain types of disease, and it is not unreasonable to assume that different types of people have different autonomic discharges.

Third, the gastrointestinal tract has three main functions: intake, retention and elimination. These are very complex functions, but in studying the complexities of biochemistry and physiology we sometimes lose sight of the functional purpose, though it is always before us.

Now our contention is this: When an individual by force of circumstances develops a gastrointestinal disorder of a psychosomatic nature, his personality constellation decides which function is going to be upset. The choice is secondary and only incidental to the function that the organ serves; for instance, the person with a peptic ulcer has a disorder of intake, the person with a mucous colitis, a disorder of elimination. Psychic patterns seem to follow function rather than anatomic differentiation, for both the ulcer and the colitis are results of parasympathetic stimulation. Either disorder can be experimentally produced by parasympathetic stimulation, and an ulcer, at least, can be alleviated by section of the vagus. Now what is the difference between an ulcer patient, on the one hand, and a colitis patient on the other? The ulcer patient has long been described as an alert, ambitious, independent fellow, aggressive in making his way in life and apparently developing his ulcer only when he feels his ambitions are being thwarted or when he is in danger of failure. Place him in the noncompetitive, secure atmosphere of a hospital and his ulcer usually heals promptly. Get him to let down on his drive and tempo and he probably will stay well.

Our patient is at the other end of the behavior table, and she is typical of the patient with mucous colitis. After reading her history, one can agree that she was passive, compliant, unaggressive and meek, and totally unable to have any open expression of hostility, even under the most provoking circumstances. Unlike the ulcer patient, who is taking from his environment the things he thinks he needs to make him happy, this woman was busy giving to others, no matter what the cost, so they would like her. These different psychic patterns must set up very different parasympathetic activity, involving separate and distinct functions. At any rate, this patient's colon must writhe within her when she feels emotions she is unable to express.

LEFT BUNDLE BRANCH BLOCK WITH SPONTANEOUS REMISSION AFTER AT LEAST THREE YEARS *

By S. L. MYRE, M.D., *Greybull, Wyoming*, and B. F. FULLER, M.D.,
St. Paul, Minnesota

It is agreed that a bundle branch block, once established, remains as a permanent abnormality for the remainder of the patient's life. While there are numerous reports of cases of functional or transient heart blocks, we found only one report of a spontaneous remission of a bundle branch block once it was established for a period of a year or more.¹

CASE REPORT

A 56 year old male was first seen on January 1, 1943. He had been in excellent health prior to this time, save for a mild upper respiratory infection of about a week's duration. On January 1, he was walking along a loading platform with two asso-

* Received for publication June 7, 1949.

ciates when he suddenly lost consciousness and fell a distance of 10 feet to the ground. He did not trip on anything, as the platform was smooth. He states the unconsciousness (or severe vertigo) was of a very transitory nature, since he can remember recovering enough to grasp at the loading platform as he fell past it, and he can remember striking the ground. Save for bruises from the fall, no ill effects were noted.

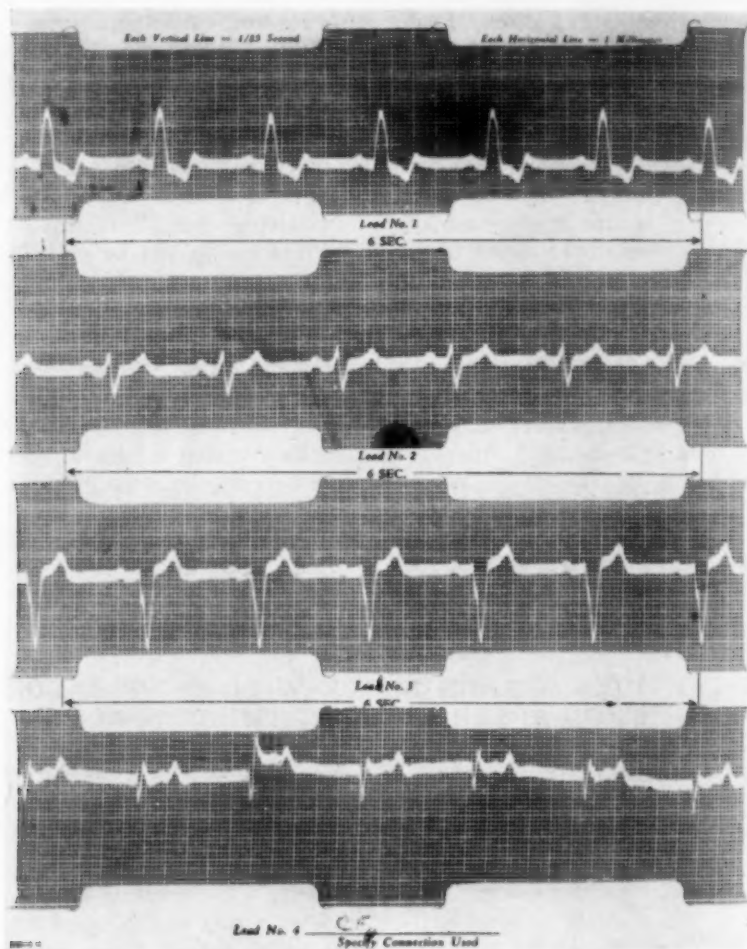


FIG. 1.

On January 26, 1943, the patient suddenly became moderately dizzy following the ingestion of a heavy meal. Because of this, he lay down on the couch for a short nap. When he suddenly awakened, he was so dizzy that he had to crawl upstairs on his hands and knees. He was seen in his home approximately an hour later by one of us (S. L. M.), and at that time the only physical or neurologic finding was a lateral nystagmus. Both the dizziness and the nystagmus persisted for about 24 hours. No tinnitus was noted.

From that time to the present the patient has been seen at intervals of from six months to a year, with the exception of the period from October, 1945, to September, 1947, and he has had no further complaints.

Past history is negative except for an extensive third degree burn of the right thigh and the lower part of the trunk in 1936 with extensive residual scarring. Otherwise, the patient had always enjoyed good health and had been moderately athletic all his life. No past history suggestive of heart disease was elicited.

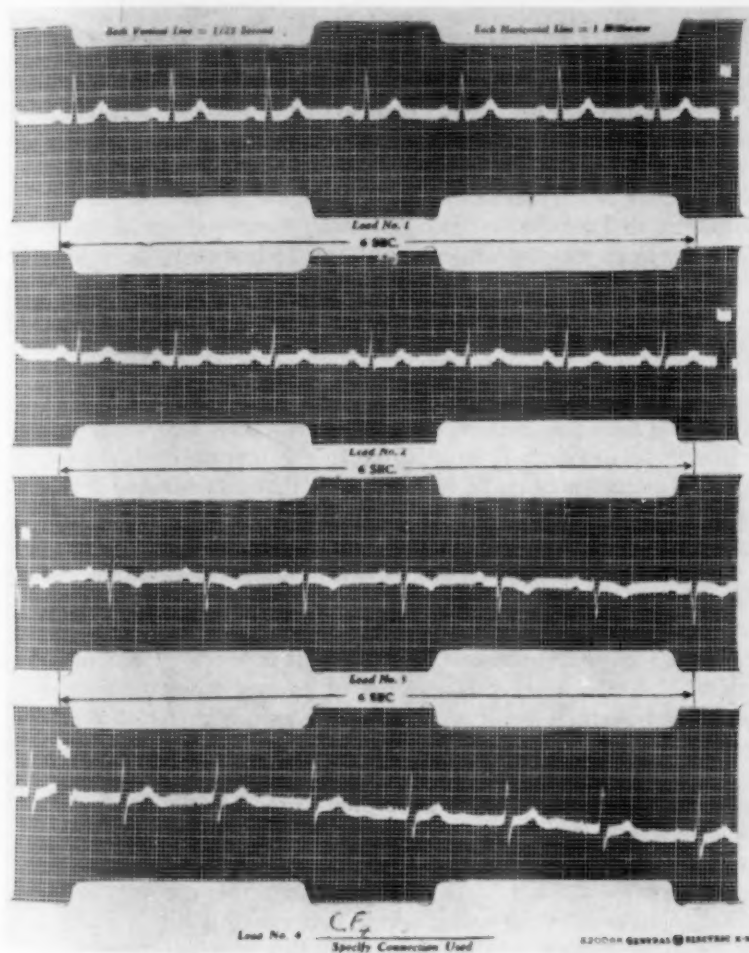


FIG. 2.

Physical examination has always been negative except for the transitory findings noted above. His blood pressure has varied from 120 to 140 systolic, and from 70 to 85 diastolic. Examination of the eyes showed normal fundi.

Laboratory studies, including routine blood and urine examinations, non-protein-nitrogen, serologic test for syphilis, blood sugar and chest roentgenogram were all negative. The only positive finding was in the electrocardiogram taken on February

10, 1943, which exhibited the left bundle branch block seen in figure 1. This persisted in an unchanged form on all tracings until the one of September, 1947, when it reverted to normal as shown in figure 2. It has remained normal and unchanged to the present time.

Unfortunately, the patient was not seen during the period from October, 1945, to September, 1947. Thus, the last abnormal tracing we have was taken in October, 1945, making the total duration of the bundle branch block as recorded on electrocardiograms two months short of three years.

COMMENT

Although there is nothing objective to substantiate our diagnosis, we feel on empiric grounds that this patient has coronary artery disease and that his electrocardiographic lesion either followed a "silent," acute coronary occlusion or that it was the result of partial destruction of the bundle branches by a slowly progressive, chronic coronary insufficiency. His age is in favor of such a diagnosis. Also, according to Yater,² a left bundle branch block is more likely to be due to arteriosclerotic heart disease while a right bundle branch block is more likely to be due to rheumatic heart disease. One could postulate that he had a coronary occlusion at the time he fell from the loading platform, but that would be purely speculative. Indeed, it is a fair possibility that he had had his bundle branch block for a long period of time before we saw him and that the discovery of it after the time of the fall was purely coincidental.

It is felt that the above case report is of interest as it represents, insofar as we have been able to ascertain from a search of the literature, the second reported instance of a permanent bundle branch block that has been seen in remission. The weight of authority supports the opinion that once a bundle branch block has become well established, it is an irreversible lesion. This opinion is based on the fact that the pathologic lesion is nearly always destruction of the bundle branches with replacement by fibrous tissue. It is also supported by the extreme rarity of seeing such a lesion reverse itself. On the basis of present day evidence there is no reason to cast doubt on this concept. Certainly our patient and the one of Kalett more probably are of interest from the point of view of their rarity than from the point of view of their casting doubt on present opinion. However, the search for an explanation of the spontaneous clearing up of their lesions stimulates interesting speculation.

Partial destruction of tissue in the region of the bundle branches and relative anoxia of the remaining tissue, both tending to cause depression of conductivity, may be the explanation. This phenomenon is seen in those patients who develop a transitory bundle branch block following an acute coronary occlusion with myocardial infarction, or following severe congestive failure. These blocks are seen to clear up during convalescence. In this specific instance, the biggest difficulty is to accept the presence of tissue anoxia sufficient to cause the depression of conductivity for three or more years, with retention of viability over the entire period, which would enable the conduction tissue to regain function once the tissue anoxia was overcome by the development of sufficient collateral circulation. Although this is pure speculation, it does find some support in the work of Yater who, in his careful anatomic study, noted that one may have a bundle branch block without complete destruction of tissue, and that one may see

fairly extensive tissue destruction in the absence of electrocardiographic evidence of block.

The only other probable hypothesis is that the conduction fibers in the region of the bundle branches were totally destroyed, and that they regenerated themselves. It is the opinion of physiologists that this tissue cannot regenerate once it is destroyed.⁴

One other point is well illustrated by this patient. As is well known, early reports of bundle branch block were all associated with a rather grim prognosis. Even at the present time, a permanent bundle branch block is generally regarded as an ominous sign, in spite of the fact that it is recognized that some patients with such lesions may live for many years after the discovery of the lesions. In general, it is stated that roughly 50 per cent of such patients die within a year or two of the discovery, but that the remaining patients may live as long as 15 to 20 years^{3, 5, 6} (although the latter expectancy is most unusual). At the present time, the prognosis of bundle branch block is thought to parallel the prognosis of the underlying heart disease, and the patients in whom the electrocardiographic lesion is found in the absence of any other evidence of heart disease are expected to live the longest. Our patient certainly tends to bear out this belief.

SUMMARY

The case of a patient with left bundle branch block of at least three years' duration followed by spontaneous recovery is reported.

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EDITORIAL

MYOCARDITIS IN POLIOMYELITIS AND RELATED VIRAL INFECTIONS

CLINICAL and epidemiological evidence indicates that poliomyelitis is a common, widespread infection which is usually restricted to the peripheral tissues and causes but little injury to the host. There is much indirect evidence that the gastrointestinal tract, including the pharyngeal mucosa, is both the portal of entry and primary locus of infection, and it is certainly the source from which the virus is disseminated. The involvement of the motor areas in the central nervous system, which causes the characteristic paralyses and has given the disease its name, is manifest only in a small proportion of the cases, and it is probably to be regarded as an incidental and relatively unusual phenomenon, analogous to the encephalitis which occasionally occurs in mumps and some other viral infections.

Attempts to prove these points directly, however, and to demonstrate the precise pathogenesis of the disease by anatomical and experimental studies have encountered technical difficulties. Anatomical studies of human material have necessarily been limited largely to the severest types of infection in which extensive damage to the nervous system has occurred. Even in these cases, however, significant lesions in extraneural tissues have been surprisingly sparse. In acutely paralyzed skeletal muscle degenerative changes in, or destruction of the motor end plates have been reported, although the precise significance of this is uncertain. The muscle fibers themselves, with one or two possible exceptions, have been singularly free from detectable alterations until the late secondary atrophy appears. In a significant number of cases, however, focal areas of myocarditis have been observed.

The first adequate report appears to be that of Saphir and Wile,¹ who observed such lesions in six of seven fatal cases. Saphir² reported a second study of 17 fatal cases in a later epidemic and observed microscopic foci of myocarditis in 10. In some the areas were sparse and minute but in others, more numerous and extensive. In the milder forms there was dilatation of the capillaries with accumulation of leukocytes in the lumen and perivascular infiltration with leukocytes and mononuclear cells. In more severe lesions there was also infiltration of the interstitial tissue with similar cells, which in two cases was described as massive. The muscle fibers were not necrotic but showed cloudy swelling, loss of striation, in places were compressed and showed a tendency to coalesce. There was no close correlation between the myocardial lesions and the clinical type of poliomyelitis. Concerning the cardiac lesions Saphir concluded: "The

¹ Saphir, O., and Wile, S. A.: Myocarditis in poliomyelitis, *Am. J. M. Sc.* 203: 781-788, 1942.

² Saphir, O.: Visceral lesions in poliomyelitis, *Am. J. Path.* 21: 99-105, 1945.

sudden death of some of these children can easily be explained by the myocarditis."

Saphir's observations have been confirmed by (among others) Peale and Lucchesi,³ who found similar focal lesions in five of seven cases; and by Dolgopol and Cragan.⁴ The latter studied material from 92 cases in the files of the Willard Parker Hospital and found focal lesions in 16. In many cases only a single section was available for study. In four of these, death was attributed to cardiac failure. The lesions were most frequent in the posterior wall of the left ventricle and the posterior papillary muscle, also in the left auricle and interventricular septum. Interstitial edema and degenerative changes in the muscle fibers of mild degree were common, with or without foci of myocarditis. The latter resembled closely those described by Saphir.

Ludden and Edwards⁵ reported a study of 35 cases, in 14 of which there was histologic evidence of myocarditis. In three, gross lesions were visible. In the milder cases the focal lesions closely resembled those previously described, although vacuolation and fragmentation of muscle fibers were more prominent. In six severe cases, however, there were areas of focal necrosis involving usually portions of one or two adjacent muscle fibers. These were accompanied by much degenerative change of less severity in the surrounding muscle and by marked congestion, edema and cellular infiltration of the interstitial tissue. More extensive areas of necrosis were occasionally found, and in one case death resulted from perforation of such an area in the posterior wall of the right atrium. Although in six cases death occurred "rather suddenly," in none of the other five could the myocarditis be definitely established as the immediate cause.

Gefter et al.⁶ have reported a clinical study of the heart in a large series of nonfatal cases of acute poliomyelitis. The most pertinent observations concern electrocardiographic studies in 226 cases. Abnormalities regarded as significant were observed in 32 (14 per cent). There was a definite correlation between these abnormalities and both the severity of the disease and the duration of the fever. They usually appeared early and persisted for several weeks. The more common abnormalities were changes in the shape of the P waves, prolonged P-R interval, deviation of the S-T segments and depression or inversion of the T waves. Tracings could not be obtained in 11 fatal cases. Six of these came to autopsy, and two showed areas of perivascular and interstitial cellular infiltration in the myocardium. Gefter's observations indicate that a derangement of myocardial function is

³ Peale, A. R., and Lucchesi, P. F.: Cardiac muscle in poliomyelitis, *Am. J. Dis. Child.* 65: 733-738, 1943.

⁴ Dolgopol, V. B., and Cragan, M. D.: Myocardial changes in poliomyelitis, *Arch. Path.* 46: 202-211, 1948.

⁵ Ludden, T. E., and Edwards, J. E.: Carditis in poliomyelitis. An anatomical study of 35 cases and review of the literature, *Am. J. Path.* 25: 357-373, 1949.

⁶ Gefter, W. T., et al.: The heart in acute anterior poliomyelitis, *Am. Heart J.* 33: 228-239, 1947.

frequent in poliomyelitis, but this manifestly does not demonstrate the existence of a myocarditis. Myocarditis has been reported in isolated cases of other viral infections, including influenza and possibly mumps, as well as in severe rickettsial infections.

Although it seems probable that the virus of poliomyelitis was the cause of the myocarditis, more direct and convincing evidence of the specific nature of these lesions might be obtained by reproducing them experimentally in animals and by demonstrating the virus in the human myocardium. Some progress has now been made along both these lines.

Experimental studies of poliomyelitis have been greatly hampered by the necessity of using monkeys. As ordinarily isolated and maintained by intracerebral injections into rhesus monkeys, the virus undoubtedly suffers alterations, presumably mutations, including an increase in virulence for these animals. In this species the infection is strictly neurotropic, and even in animals infected by other routes, extraneural lesions are rarely found.

The usual laboratory rodents ordinarily can not be infected by virus from human sources. In most cases attempts to infect them with strains of virus which have been established in monkeys have also been unsuccessful. This has been accomplished in a few instances, however, by serial intracerebral injections in hamsters or cotton rats and subsequently in white mice. The most carefully studied example is the Lansing strain (Armstrong, 1939). These "murine" strains suffer further alterations in the process of adaptation to rodents. They become more pathogenic for mice and lose more or less their virulence for monkeys. There is at least a suspicion that they may undergo some change in antigenic structure, although they retain a close relationship to the original human strain. Like most of the simian strains, they are neutralized by the sera of a majority of cases convalescent from poliomyelitis as well as by most "normal" adult human sera. They continue to be strictly neurotropic, and except for the neurologic manifestations the disease in mice has little resemblance to that in man.

Jungeblut and Sanders,⁷ working with a simian strain of poliomyelitis virus (SK) originally obtained from the feces of an abortive human case, reported establishing the virus in white mice after preliminary passages in cotton rats in three series of experiments. This strain, now known as the Columbia (Col) SK virus, although similar in many ways to the usual simian and murine-adapted strains of poliomyelitis virus, is antigenically distinct and differs from them substantially in pathogenicity.⁸ Col SK virus is highly pathogenic for mice, infecting them by any route of inoculation, including oral administration. The animals typically develop flaccid paralysis and show lesions in the brain and cord described as typical of poliomyelitis in these animals. The virus also invades the per-

⁷ Jungeblut, C. W., and Sanders, M. J.: Studies of a murine strain of poliomyelitis virus in cotton rats and white mice, *J. Exper. Med.* **72**: 407-436, 1940.

⁸ Jungeblut, C. W.: Further experiments with Columbia Sk murine poliomyelitis virus, *Bull. New York Acad. Med.* **26**: 571-577, 1950.

ipheral tissues generally, is found in the blood and is excreted in the feces. In many animals, focal areas of myocarditis occur, similar to those described in human cases. The paralyzed skeletal muscles usually show no lesion, but if the virus is injected into the muscle, a severe myositis may be produced,⁹ followed quickly by the appearance of typical poliomyelitic lesions of the corresponding segment of the cord. The process may extend to other areas in the central nervous system, but the muscles secondarily paralyzed show no myositis.¹⁰

If the Col SK virus is carried through a series of mice by intracerebral injections, it tends to lose its viscerotropic properties and cause only neurologic lesions.¹¹ If it is carried by intraperitoneal injections, using spleen as the inoculum, its viscerotropic properties are restored or enhanced, and the paralyzed skeletal muscles as well as the myocardium may show myositis, sometimes almost as extensive as that caused by the Coxsackie viruses.¹²

Rhesus monkeys are highly but not completely resistant and rarely show paralyzes. If Col SK virus is injected intracerebrally into cynomolgus (Javan) monkeys, however, paralyzes and typical poliomyelitic lesions are readily produced. Such animals also often show myocarditis. Cercopithecus monkeys are also susceptible. They seemed less likely to develop paralyzes, but the myocardial lesions are described as unusually extensive and severe.⁸

At least three essentially identical strains¹³ of virus have been isolated from other sources. Toomey,¹⁴ in experiments largely duplicating Jungeblut's, obtained from SK virus a strain (MM) indistinguishable from Col SK virus. (Melnick,¹⁵ however, in a similar experiment, obtained a strain (Y-SK) resembling the Lansing virus and different from Col SK virus.)

A virus known as EMC (encephalomyocarditis) virus was isolated in mice by Helwig and Schmidt¹⁶ in Florida from the myocardium of a stock chimpanzee which had died unexpectedly and showed an extensive myocarditis. It caused in mice the usual paralyzes and poliomyelitic lesions, but when first isolated the myocardial lesions were especially prominent.

A fourth strain—Mengo virus—was isolated by Dick et al.¹⁷ in Uganda

⁸ Rustigian, R., and Pappenheimer, A. M.: Myositis in mice following intramuscular injection of viruses of the mouse encephalitis group and of certain other neurotropic viruses, *J. Exper. Med.* **89**: 69-92, 1949.

¹⁰ Jungeblut, C. W.: Newer knowledge on the pathogenesis of poliomyelitis, *J. Pediat.* **37**: 109-128, 1950.

¹¹ Jungeblut, C. W., and Steenberg, E.: Neurotropic and viscerotropic strains of Columbia SK and encephalomyocarditis virus, *Arch. Path.* **49**: 574-581, 1950.

¹² Editorial: Coxsackie viruses, *Ann. Int. Med.* **34**: 257-263, 1951.

¹³ Warren, J., Smadel, J. E., and Russ, S. B.: The family relationship of encephalomyocarditis, Columbia SK, MM, and Mengo viruses, *J. Immunol.* **62**: 387-398, 1949.

¹⁴ Toomey, J. A., and Takacs, W. S.: Experiments with the SK strain of poliomyelitis in smaller animals, *J. Bact.* **43**: 87, 1942.

¹⁵ Melnick, J. L., and Ward, R.: Adaptation of poliomyelitis strains to rodents, with a word on nomenclature, *Federation Proc.* **7**: 308, 1948.

¹⁶ Helwig, F. C., and Schmidt, E. C. H.: A filter-passing agent producing interstitial myocarditis in anthropoid apes and small animals, *Science* **102**: 31-33, 1954.

¹⁷ Dick, G. W. A., Smithburn, K. C., and Haddow, A. J.: Mengo encephalomyelitis virus. Isolation and immunological properties, *Brit. J. Exper. Path.* **29**: 547-558, 1948.

from two stock rhesus monkeys (spontaneous infections), from a mongoose and from pools of trapped mosquitoes. It was also isolated from a human subject with "mild encephalitis" who probably acquired the infection accidentally in the laboratory.

That these viruses can cause human infection is also indicated by the observations of Smadel and Warren.¹⁸ Convalescent sera from 11 of 44 cases of "three day fever" clinically diagnosed as aseptic meningitis or abortive poliomyelitis, occurring in military personnel in Manila (1946), showed neutralizing power for the EMC strain. Such activity was infrequent in serum from patients convalescent from poliomyelitis and rare in normal human sera.¹⁹ There is no evidence that these viruses cause infantile paralysis in man.

These recent studies emphasize the remarkable lability and adaptability of all these viruses, human and rodent, to changes of environment. They indicate the need of caution in applying to human poliomyelitis conclusions based on the animal experiments, whether with monkeys or with rodents.

The exact relationship of the Col SK virus group to human poliomyelitis virus is still unsettled. As pointed out by Jungeblut they are intermediate between the human virus and the Cocksackie viruses, from which also they are antigenically distinct. Their widespread geographic distribution as well as the circumstances under which they were isolated support the view that they are probably not recent mutants of human strains but that in nature they are rodent viruses which only exceptionally attack man.¹³ In many respects, however, the disease produced by the Col SK virus parallels human poliomyelitis more closely than does the disease produced in rhesus monkeys by the human virus, particularly in the generalized distribution (pantropic properties) of the virus, in the myocardial involvement and in the late invasion of the nervous system after extraneural inoculation. There is as yet no proof that all cases of infantile paralysis are due to a single "species" of virus, and even among strains of human origin that are generally accepted as "true" poliomyelitis viruses, marked antigenic differences exist. Whether these viruses of the Col SK group should be classified in a group of "poliomyelitis viruses" is a matter of opinion and definition. The Committee on Nomenclature of the National Foundation for Infantile Paralysis has held that they should not.²⁰

Additional evidence of the generalized nature of the human infection has recently been obtained by Jungeblut and Stevens.²¹ In one human case of 13 tested they demonstrated virus in acutely paralyzed skeletal muscle

¹⁸ Smadel, J. E., and Warren, J.: The virus of encephalomyocarditis and its apparent causation of disease in man, *J. Clin. Investigation* 26: 1197, 1947 (abstract).

¹⁹ Jungeblut, C. W.: Neutralization of Columbia-SK and Yale-SK virus by polioconvalescent and normal human sera, *Arch. Pediat.* 67: 519-530, 1950.

²⁰ Committee on Nomenclature of the National Foundation for Infantile Paralysis: A proposed provisional diagnosis of poliomyelitis virus, *Science* 108: 701-705, 1949.

²¹ Jungeblut, C. W., and Stevens, M. A.: Attempts to isolate poliomyelitis virus from the paralyzed muscle of patients during the acute stage of the disease, *Am. J. Clin. Path.* 20: 701-706, 1950.

by intracerebral inoculation into cynomolgus monkeys. Several animals showed flaccid paralyses with typical poliomyelitic lesions in the cord. Two showed myocarditis. In one monkey inoculated intramuscularly with virus from the cord of a paralyzed monkey, flaccid paralysis of this leg appeared 14 days later, and histologic examination showed an extensive myositis with necrosis of muscle fibers and a severe poliomyelitic lesion limited to the corresponding segment of the cord. Virus was demonstrated in the paralyzed muscle of this monkey. This experiment, therefore, essentially duplicated that with Col SK virus described above.

Jungeblut^{8, 22} has also reported demonstrating virus in the myocardium of three of five human cases of poliomyelitis by intracerebral injection into cynomolgus monkeys. One of these hearts showed extensive myocarditis, but the others did not. In two of these cases virus was also isolated from the cord. In addition to typical poliomyelitic lesions several animals showed either outspoken myocarditis or early necrosis in the myocardium. No myositis could be demonstrated in paralyzed skeletal muscles. Two freshly isolated strains of virus were completely inactivated by pooled serum from patients convalescent from poliomyelitis, and serologically they resembled the Brunhilde strain of human poliomyelitis virus.

The route by which the virus reaches the myocardium is not known. Although it is reasonably certain that the central nervous system is invaded by centripetal passage of the virus through the nerve trunks, in the case of the myocardium the blood seems a more probable pathway. Direct evidence for this is virtually lacking. In isolated instances, however, demonstration of the virus in the blood has been reported in the earliest stage of the infection in man^{23, 24} as well as in monkeys,²⁵ and the possibility of a viremia in the prodromal or initial stage has not been entirely excluded. That the lymphoid tissue is invaded seems highly probable. Hyperplasia and an inflammatory reaction of nonspecific character have been described by a number of observers, including recently Sommers et al.²⁶ who found them in 41 of 50 human cases examined.

One may conclude that a disturbance of myocardial function is common in severe poliomyelitis and that actual myocarditis is frequent in fatal cases if these are examined with sufficient care. That the myocarditis is caused by the virus is indicated by the failure clinically to find any other satisfactory

²² Jungeblut, C. W.: A preliminary note on the isolation of human poliomyelitis virus from the heart of fatal cases of the disease, Third European International Poliomyelitis Conference, Amsterdam, May 30-June 2, 1950.

²³ Ward, R., Horstman, D. M. and Melnick, J. L.: The isolation of poliomyelitis virus from human extraneural sources. IV. Search for virus in the blood of patients, *J. Clin. Investigation* 25: 284-286, 1946.

²⁴ Koprowski, H., et al.: Isolation of poliomyelitis virus from human serum by direct inoculation into a laboratory mouse, *Pub. Health Rep.* 62: 1467-1476, 1947.

²⁵ Melnick, J. L.: Poliomyelitis virus in the blood stream in the experimental disease, *Proc. Soc. Exper. Biol. and Med.* 58: 14-16, 1945.

²⁶ Sommers, S. C., Wilson, J. C., and Hartman, F. W.: Lymphoid lesions in poliomyelitis, *J. Exper. Med.* 93: 505-512, 1951.

explanation and also by the production of similar lesions with human virus in suitable experimental animals as well as by the demonstration of the virus in the human myocardium.

Further study will be required to determine the practical clinical importance of the myocarditis. Thus far substantially all the cases recognized have been in severely paralyzed patients with bulbar lesions, in whom death is usually attributed to respiratory failure. It seems probable that in some patients who have died in spite of the use of a respirator, circulatory failure secondary to myocardial damage may have been the immediate cause of death. Even more interesting is the light these observations shed on the nature of the disease in man.

P. W. C.

REVIEWS

Verdaunungs- und Stoffwechselkrankheiten. By Dr. med. MAX BÜRGER, ord. Professor der Medizin, Direktor der Medizinischen Univ.-Klinik, Leipzig. 439 pages; 18 × 26 cm. Ferdinand Enke Verlag, Stuttgart. 1951. Price, geheftet DM 55.-; gebunden DM 59.-

This new text on Digestive and Metabolic Diseases was prepared upon the publisher's special request that the author write a book for students and younger physicians, stressing chiefly the practical aspects of training and abstaining as much as possible from "theoretical speculations and hypotheses." The author, looking back upon almost 40 years of clinical experience and academic teaching, has accomplished this task in a very competent manner. Without actually neglecting the theoretical basis, for which, besides, a more extensive work of the same author is available (*Einführung in die pathologische Physiologie*, 3rd Ed., 1949), the clinical picture is emphasized and most impressively presented here, as it appears to a keen observer and a deeply searching physician with widespread interests.

The material has been arranged in 24 main chapters, excellently aided by 123 (including 43 colored) illustrations and 73 tables. An attempt has been made to extend the concept of metabolic diseases farther than was customary heretofore and to include especially the relations of metabolism to diseases of the skin, the musculature and the nervous system. Also the relations between gastrointestinal and hematological diseases have been duly stressed.

The style is that of an experienced lecturer using short sentences throughout. Personal experiences and opinions are freely expressed. The bibliography at the end of each chapter has been kept purposely short, giving the student an introduction to more detailed studies. This could be supplemented for interested readers outside Germany, because occasionally authors and their interesting observations are cited without a specific reference.

Events due to World Wars I and II and the recent postwar-period have left their mark. The consequences of starvation and prolonged malnutrition have been thoroughly investigated and masterfully described. Recent therapeutic advances due to the application of the newer members of the vitamin B-complex (folic acid, vitamin B₁₂) or of the adrenal cortical hormone series (cf. cortisone) have not received adequate coverage, chiefly because these compounds were not available in Germany in sufficient quantities for clinical evaluation and practical prescribing. Likewise parenteral fluid therapy has admittedly not yet the variety of injectable solutions at its disposal which has been put into the hands of the American physician. Certain German mortality figures quoted, as for diabetic coma and gallbladder surgery, appear comparatively high.

Time conditioned shortcomings as these, however, do not detract materially from the great didactic value which is represented by the book as a whole.

ERNEST BRUCH, Ph.D., M.D.

Principles of Internal Medicine. By T. R. HARRISON, M.D. (Editor-in-Chief); with PAUL B. BEESON, M.D., WILLIAM H. RESNIK, M.D., GEORGE W. THORN, M.D., M. M. WINTROBE, M.D., and 48 contributing authors. 1590 pages with 245 illustrations; 20 × 27 cm. The Blakiston Company, Philadelphia. 1950. Price, \$12.00.

The aim of this book is to integrate preclinical sciences with clinical medicine. Reviewers would have an easy task if the work had been divided into two, approximately equal-sized volumes instead of being served up in one unmanageable tome. It would then have been possible to recommend with enthusiasm the first volume, and to shrug one's shoulders about the second. As it is, however, the text cannot be parcelled. You must have all eight and one-half pounds of the book or nothing. And it is difficult indeed to decide whether the excellence of the first half can carry the mediocrity of the second.

As the arrangement of this text is unconventional, it is necessary to outline the contents. The book consists of seven parts. Part I deals with Cardinal Manifestations of Disease—pain; weakness; shortness of breath and cough; disturbances in circulation; indigestion and jaundice; polyuria, oliguria, uremia and edema; alterations in weight; anemia, bleeding and lymphadenopathy. Part II discusses Physiological Considerations—inheritance and aging; neoplastic diseases; fluid and electrolyte balance; intermediary metabolism; electrophysiology; and normal emotional development. Part III is occupied with Reactions to Stress and to Antigenic Substances. Part IV presents Metabolic and Endocrine Disorders—nutritional and hormonal disturbances, metabolic disorders of bone, disorders of muscle, and inborn errors of metabolism. Part V is devoted to Disorders due to Chemical and Physical Agents. This takes the text to page 770 and it is at this point that one could wish that the authors had laid down their pens.

These first five parts are much to be praised. In general the topics discussed are dealt with in masterly fashion, the result being a series of excellent essays on pathological physiology. At times the meaning is cloaked in unnecessary verbiage, however. In the editors' words these sections of the book deal with the "functional approach to the principles of internal medicine." They should prove a godsend to clinicians preparing correlative lectures for second year students.

The last two parts of the book are devoted to Diseases due to Biologic Agents and Diseases of Organ Systems—that is to say they embrace most of the usual syllabus of a standard textbook of medicine. These closing cadences, however, are characterized by a diminuendo in quality; for this more conventional half of the book is no better than most other available texts, and it is inferior to many. Accounts of diseases as such are often sketchy and inadequate, making the book a poor work of reference and defeating one of the editors' stated purposes—to provide "thorough familiarity with common disorders."

The book is intended mainly for students and for physicians who "desire a presentation of the important scientific principles that are necessary for a rational understanding of the development, evolution, and management of internal diseases." One is forced to the conclusion that the authors have bitten off more than they can satisfactorily chew.

H. J. L. M.

Symposium on the Healthy Personality. Edited by MILTON J. E. SENN, M.D., Departments of Pediatrics and Psychiatry, School of Medicine, Yale University. 298 pages; 15.5 × 23.5 cm. Josiah Macy, Jr., Foundation, New York. 1950. Price, \$2.50.

This volume represents an important contribution made by the Josiah Macy, Jr. Foundation to the Fact Finding Committee of the Midcentury White House Conference on Children and Youth. That Conference, held December 1950, stated as its purpose, "to consider how we can develop in children the mental, emotional, and spiritual qualities essential to individual happiness and responsible citizenship, and what physical, economic and social conditions are deemed necessary to this development."

This volume contains three papers that were used as the basis of discussion. These papers were: "Growth and Crises of the 'Healthy Personality'" by Erik H. Erikson of the University of California; "Constitutional and Prenatal Factors in Infant and Child Health" by M. F. Ashley Montague of Rutgers University; and "Toward a Social Psychology of Mental Health" by Marie Jahoda of New York University. Two Symposia were held in June and July 1950, each lasting two days, during which leaders in various fields related to child health and development were gathered from all over the country to discuss these topics. The rest of the volume is devoted to a verbatim account of these discussions.

This volume is primarily of value to other leaders in the field of child health and development. It is confusing to those who are not experts to discover the amount of disagreement that can occur in such a young science. The discussion illustrates the need for a great deal of basic research to decrease the areas where disagreement occurs. Readers who are not expert in this field would do better to obtain the Fact Finding Report which was finally produced by the White House Conference.

H. W. N.

The Management of the Patient with Severe Bronchial Asthma. By MAURICE S. SEGAL, M.D., Assistant Professor in Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts. First Edition. 158 pages; 14 x 22.5 cm. Charles C. Thomas, Springfield, Illinois. 1950. Price, \$3.50.

Dr. Segal has had a great deal of experience in the handling of severe asthma and has written extensively on the use of aerosolized medicaments in its control. This book represents a definite contribution to the subject and a correlation and evaluation of the measures available that are of value to men concerned with the treatment of these seriously ill patients.

The author discusses "protection studies" at length. One of the greatest difficulties in evaluating the effect of antiasthmatic preparations, particularly their bronchodilating qualities, has been the impossibility of evaluating their effect upon the patient's symptoms because of the lack of measured and objective ways to determine results. The method is to administer bronchospastic agents, namely, histamine or mecholyl chloride to produce bronchospasm. Vital capacity estimations done before and after the administration of these agents provide a way in which to determine their effects. Because this is an objective procedure and because it can be done at will, it has been valuable in measuring the bronchodilator effects of the various therapeutic agents used in asthma.

The author discusses, at length, the effectiveness of these agents as determined by this method. However, the reviewer is not entirely convinced that these results completely parallel clinical ones.

The general content of the book relative to the symptomatic control of severe asthma is satisfactory, particularly the rather detailed consideration of aerosol therapy. The reviewer is of the opinion that the author has achieved beneficial results with antihistaminics in asthma that have been better than those of other observers.

Further, several opinions of the author seem open to question. He states that "the use of the hypodermic needle for self-medication, which should be avoided, is too often encouraged." Actually, the reviewer's experience is such that it leads him to believe that this procedure is most useful if the patient is properly trained and if the disadvantages of overuse are sufficiently stressed. In addition, the author states that Demerol (meperidine hydrochloride) is a far safer drug than morphine, is more efficacious, and is extremely helpful in relieving intractable cough. The reviewer's

experience is contrary to this because three deaths are known to have occurred within one year, apparently, as the result of the administration of Demerol and, further because addiction is a definite possibility that renders the use of such a preparation in a chronic condition open to serious question.

As a guide to physicians interested in the subject, however, the over-all approach is of value and should be helpful in the management of these cases.

H. M. B.

Fundamentals of Clinical Fluoroscopy, with Essentials of Roentgen Interpretation.

By CHARLES B. STORCH, M.D., Adjunct, Radiodiagnostic Department and Radiotherapy Department, Beth El Hospital, Brooklyn, N. Y. 196 pages; 18 × 26 cm. Grune and Stratton, New York. 1951. Price, \$6.75.

Fluoroscopy is a valuable diagnostic procedure. It is employed not only by the roentgenologist, but also by various medical specialists and even by the general practitioner. Those of the first group have specialized training, and comprehensive texts are directed to their needs. The members of the second group frequently have experience and training in fluoroscopy as applied to their limited fields, such as cardiology or gastroenterology. Those of the third group all too often employ the fluoroscopic method without adequate training, and it is therefore all the more unfortunate that heretofore no adequate text has been available for them.

This volume "is intended only as background: to give the basic knowledge, to indicate the capacities and limitations of the method and many practical hints gleaned from clinical experience, to develop an informed and logical approach, and to make the actual learning process easier." Within the limits of this statement, this book goes far to accomplish its author's aims. The material is clearly presented. The illustrations are excellent. This text provides enough information to enable the medical specialist and general practitioner to consider intelligently the fluoroscopic reports rendered them by *others*, and to realize the potentialities and limitations of the fluoroscopic method. This book is highly recommended for this purpose. Its perusal does not, of course, qualify an untrained person to render a competent opinion on either cardiac or gastrointestinal fluoroscopic findings as an *original observer* where his observations may be used as a basis for important decisions regarding a patient. This does not detract from the undoubted value of this work, properly used. As the author states, "This book, together with proper clinical training, should make (the fluoroscopic) examination more valuable." It will prove profitable reading for medical students, interns and residents, as well as the groups mentioned above.

S. S.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annotated Bibliography of Vitamin E—1940 to 1950. Compiled by PHILIP L. HARRIS and WILMA KUJAWSKI, of The Research Laboratories of Distillation Products Industries (Division of Eastman Kodak Company). 184 pages; 27.5 × 21 cm. (paper-bound). 1951. National Vitamin Foundation, New York. Price, \$3.00.

Behandlung diabetischer Kinder. By PRIV.-DOZ. DR. KARLA WEISSE. 72 pages; 21 × 15 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart. Price, DM 4.90.

- Behandlung innerer Krankheiten.* By PROF. DR. FERDINAND HOFF. 41 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart.
- Clinical Heart Disease.* 4th Ed. By SAMUEL A. LEVINE, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School, etc. 556 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, \$7.75.
- Diabetes Insipidus.* (Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work.) By HARRY BLOTNER, M.D., Associate Visiting Physician, Beth Israel Hospital, Boston; Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. 190 pages; 24.5 × 16 cm. 1951. Oxford University Press, New York. Price, \$4.50.
- Electroencephalography in Clinical Practice.* By ROBERT S. SCHWAB, M.D., Director of the Brain Wave Laboratory, Massachusetts General Hospital, and Associate in Neurology, Harvard Medical School. 195 pages; 25.5 × 16.5 cm. 1951. W. B. Saunders Company, Philadelphia. Price, \$6.50.
- Growth and Development of Children.* By ERNEST H. WATSON, M.D., Associate Professor, and GEORGE H. LOWREY, M.D., Instructor, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School. 260 pages; 23.5 × 15 cm. 1951. The Year Book Publishers, Inc., Chicago. Price, \$5.75.
- Herschalldiagnostik in Klinik und Praxis.* By JÖRGEN SCHMIDT-VOIGT. 116 pages; 21 × 14.5 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart. Price, DM 9.60.
- Hypertension: A Symposium Held at the University of Minnesota on September 18, 19, and 20, 1950, in Honor of Elexious T. Bell, M.D., Benjamin Clawson, M.D., and George E. Fahr, M.D.* 573 pages; 24 × 16 cm. 1951. University of Minnesota Press, Minneapolis. Price, \$7.50.
- The Kidney: Structure and Function in Health and Disease.* By HOMER W. SMITH, A.B., Sc.D., M.S., Professor of Physiology, New York University College of Medicine. 1049 pages; 24 × 15.5 cm. 1951. Oxford University Press, New York. Price, \$12.50.
- The Newspaper Press Directory and Advertisers' Guide, 1951—Centennial Issue.* 600 pages; 29.5 × 21.5 cm. 1951. Benn Brothers, Limited, London. Price, £2.2s (postage 1s.6d. extra).
- The Physiology and Pathology of Hemostasis.* By ARMAND J. QUICK, Ph.D., M.D., Professor of Biochemistry, Marquette University School of Medicine. 188 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, \$4.00.
- Radium Therapy: Its Physical Aspects.* 2nd Impression. By C. W. WILSON, M.Sc., Ph.D., F.Inst.P., Physicist in the Department of X-Ray and Radium Therapy, Westminster Hospital. 224 pages; 22.5 × 14 cm. 1948. Chapman and Hall, Ltd., London; Distributors in U. S. A.: The Sherwood Press, Washington 13, D. C. Price, \$6.00.
- The Social Consequences of Pneumoconiosis Among Coalminers in South Wales.* Medical Research Council Memorandum No. 25. By P. HUGH-JONES and C. M.

FLETCHER. 54 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 1s. 9d.

A Study of Epilepsy in Its Clinical, Social and Genetic Aspects. (From the Laboratory N:R 2 for Human Genetics of the Psychiatric Clinic of the Caroline Institute, Stockholm; Head: Carl Henry Alström, M.D.) By CARL HENRY ALSTRÖM. 284 pages; 24 × 16.5 cm (paper-bound). 1950. Ejnar Munksgaard, Copenhagen.

Die Untersuchung und Beurteilung der Röntgenologischen Herzgrösse. By HERMANN RAUTMANN. 144 pages; 23 × 16 cm. (paper-bound). 1951. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch. DM 18.-; geb. DM 20.-

COLLEGE NEWS NOTES

A.C.P. NOMINATING COMMITTEE FOR 1951-52

In accordance with provisions of the Constitution and By-Laws, President M. C. Pincoffs has appointed the following to the Committee on Nominations for 1951-1952:

Regents: A. B. Brower, Dayton, Ohio, Chairman; Charles F. Moffatt, Montreal, Que.

Governors: Thomas P. Findley, New Orleans; Benjamin F. Wolverton, Cedar Rapids, Iowa.

Fellow-at-large: Wetherbee Fort, Baltimore, Md.

A.C.P. POSTGRADUATE COURSES, AUTUMN, 1951

The Advisory Committee on Postgraduate Courses of the American College of Physicians announces, on page 1517, the schedule for the Autumn of 1951. It is possible that the dates of one or two of the proposed courses may be altered but that is not foreseeable at this time.

Where facilities are available, these courses will be open to non-members with adequate preliminary training. However, by direction of the Board of Regents, registration from non-members of the College may not be accepted more than three weeks in advance of the opening of any course, thus to accommodate members first.

The tuition fee in all instances will be \$30.00 per week to members; \$60.00 per week to non-members, payable in advance.

The detailed Postgraduate Bulletin, outlining each of these courses, will be published during early July and will be distributed to all members of the College and to all non-members whose names are presently on the mailing list.

For further details, registration forms, etc., address the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

A.C.P. CHANGES PROCEDURE FOR PROPOSING NEW MEMBERS

The Board of Governors of the American College of Physicians, at its meeting in St. Louis on April 11, approved a motion to change the procedure for handling of membership proposals. Proposals, in the future, along with the sponsoring letters of proposers and seconders, are to be submitted to the Governors in duplicate. The originals of the proposals and letters will be forwarded by the Governors to the Executive Secretary in Philadelphia for review by the Committee on Credentials. The copies are to be retained by the Governors for their reference files.

AUTUMN, 1951, MEETING, A.C.P. REGENTS AND COMMITTEEMEN

The regular autumn meeting of the Board of Regents and Committees of the American College of Physicians will be held at the Headquarters at Philadelphia, Pa., November 17-18, 1951.

Candidates for membership must be proposed 60 days in advance, or by September 18, for action at this meeting.

NEW LIFE MEMBERS

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. J. Burns Amberson, New York, N. Y.
 Dr. Arthur A. Holbrook, Milwaukee, Wis.
 Dr. Harold J. Brumm, St. Joseph, Mo.
 Dr. John C. Ruddock, Glendale, Calif.
 Dr. Harold Levy, Brooklyn, N. Y.
 Dr. Oscar F. Rosenow, Columbus, Ohio
 Dr. Raymond Charles Ryan, Jamaica, N. Y.
 Dr. David Gelfand, Philadelphia, Pa.
 Dr. Harvey Lester Myers, Cedarhurst, N. Y.
 Dr. Benjamin Kondo, Los Angeles, Calif.
 Dr. Henry Arthur Grennan, Washington, D. C.
 Dr. M. J. Madonick, New York, N. Y.
 Dr. O. Alan Rose, New York, N. Y.
 Dr. Morris W. Stroud, 3rd, Philadelphia, Pa.
 Dr. Nathan W. Chaikin, New York, N. Y.
 Dr. Ng William Hing, Flint, Mich.
 Dr. William B. Coen, Springfield, Mass.

FULL SET, ANNALS OF INTERNAL MEDICINE, AVAILABLE

Rarely are full sets of the ANNALS OF INTERNAL MEDICINE available from Volume I, No. 1, July, 1927. Dr. I. M. Rabinowitch, F.A.C.P., Medical Arts Bldg., Montreal 25, Que., Canada, offers his full set for sale.

ORAL EXAMINATION, AMERICAN BOARD OF PEDIATRICS

The American Board of Pediatrics announces that oral examinations will be held in Buffalo, N. Y., October 26, 27, and 28, 1951.

The Michael Reese Hospital Postgraduate School will present two two-week postgraduate courses during July. From 9 to July 21 an intensive course, "Diseases of the Endocrines—Physiology and Diagnostic Methods," will be presented. Dr. Rachmiel Levine, Director, Department of Metabolic and Endocrine Research, is coördinator of the course.

From July 23 to August 4 a full-time course in "Hematologic Diagnosis" will be presented under the direction of Dr. Karl Singer.

Further information on both of these courses may be obtained by addressing Dr. Samuel Soskin, F.A.C.P., Dean, 29th St. & Ellis Ave., Chicago 16, Ill.

A course in Postgraduate Gastro-enterology will be presented by The National Gastroenterological Association in Chicago, Ill., September 20-22, 1951. The course will be under the direction and co-chairmanship of Dr. Owen H. Wangensteen, Professor of Surgery of the University of Minnesota Medical School. Dr. I. Snapper, Director of Medical Education of The Mt. Sinai Hospital, New York, N. Y., will serve as medical coördinator. For further information and enrollment, write to the National Gastroenterological Association, Department GSJ, 1819 Broadway, New York 23, N. Y.

The Second International Gerontological Congress will be held in St. Louis, Mo., September 9-14, 1951. Sponsors of this Congress, which has the approval of the Council for the Coördination of International Congresses of Medical Sciences, are The International Association of Gerontological Societies, The Gerontological Society,

	September					October					November					December				
	3-8	10-15	17-21	24-29	1-6	8-13	15-20	22-27	29-31	5-10	12-17	19-24	26-31	3-8	10-15	17-22	24-31	Christmas Week		
Course No. 1, INTERNAL MEDICINE WITH EMPHASIS ON PATHOLOGICAL PHYSIOLOGY: University of Cincinnati College of Medicine, Cincinnati, Ohio; Marion A. Blankenhorn, M.D., F.A.C.P., Director.			X																	
Course No. 2, INTERNAL MEDICINE: Marquette University School of Medicine, Milwaukee, Wis.; Maurice Hardgrove, M.D., F.A.C.P., Director.						X														
Course No. 3, DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernestene, M.D., F.A.C.P., Director.								X												
Course No. 4, CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director.										X										
Course No. 5, ELECTROCARDIOGRAPHY: Emory University School of Medicine, Emory University, Ga.; R. Bruce Logue, M.D., F.A.C.P., Director.										X										
Course No. 6, GASTRO-ENTEROLOGY: Tulane University of Louisiana School of Medicine, New Orleans, La.; Gordon McHardy, M.D., F.A.C.P., Director.											X									
Course No. 7, RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: Massachusetts General Hospital, Boston, Mass.; Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., F.A.C.P., Co-Directors.											X									
Course No. 8, CARDIOVASCULAR DISEASES: University of Texas School of Medicine, Galveston, Tex.; George R. Herrmann, III, M.D., F.A.C.P., Director.															X					
Course No. 9, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director.															X					

Inc., and The American Geriatrics Society. The American College of Physicians is one of the coöperating organizations. Further details may be obtained by writing Dr. E. V. Cowdry, Washington University School of Medicine, St. Louis 10, Mo.

The Omaha Mid-West Clinical Society will hold its 19th Annual Assembly October 29–November 2, 1951. Among the distinguished guests will be Dr. Edward W. Boland, F.A.C.P., Los Angeles, Calif., Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., and Dr. Henry W. Brosin, F.A.C.P., Chicago.

The American Heart Association held its Annual Meeting and Scientific Sessions in Atlantic City, N. J., June 6–10. Chairmen of each of the four sessions included Dr. Howard B. Sprague, F.A.C.P., Brookline, Mass., President of the American Heart Association; Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Md., Chairman, Program Committee; Dr. T. Duckett Jones, Chairman, American Council on Rheumatic Fever; and Dr. A. C. Corcoran, Cleveland, Ohio, a member of the Section on Circulation of the Scientific Council.

The Illinois State Medical Society met in Chicago, May 22–24, under the presidency of Dr. Harry M. Hedge, F.A.C.P., Chicago. Among the guest speakers on the program were Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, "The Practicing Physician and Public Health"; Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., "Evaluation of Antibiotic Therapy"; and Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "Coronary Artery Disease."

The Association of American Physicians met in Atlantic City, N. J., May 1–2. The speaker at the dinner on May 1 was Dr. C. Sidney Burwell, F.A.C.P., Research Professor of Clinical Medicine, Harvard Medical School.

The Medical Society of the State of North Carolina held its annual meeting in Pinehurst, May 7–9. Dr. Maurice C. Pincoffs, M.A.C.P., President of The American College of Physicians, spoke on "Maryland's Medical Program for the Indigent." Among the other guest speakers were Dr. Robert H. Flinn, F.A.C.P., Washington, D. C., "The Physician's Role in Civil Defense," and Dr. Howard A. Rusk, F.A.C.P., New York, N. Y., "Medicine, Mobilization and Manpower."

The annual session of the State Medical Association of Texas was held in Galveston, May 1–2. Featured on the program were clinical luncheons at which various physicians acted as experts to whom questions were addressed. Among those who participated in the General Practice, Medicine and Pediatrics luncheon was Dr. Henry M. Winans, F.A.C.P., Dallas.

The second of a series of three one-day meetings on graduate education was held in Charleston, W. Va., May 16, under the sponsorship of the West Virginia University School of Medicine and the Committee on Medical Education of the West Virginia State Medical Association. Among the guest speakers on the program were Dr. J. Murray Kinsman, F.A.C.P., Louisville, Ky., "Relation of the Kidney to Hypertension"; Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, Pa., "New Concepts of Electrolyte Balance"; and Dr. George E. Wakerlin, F.A.C.P., Chicago, Ill., "Significance of Albuminuria, and Methods of Diagnosis and Treatment of Uremia."

The Pennsylvania Hospital, Philadelphia, held its 200th Anniversary Celebration May 2-4. A complete scientific program was presented, and included on the program were two Masters and eleven Fellows of the College. The Masters were Dr. Elliott P. Joslin, Boston, and Dr. O. H. Perry Pepper, Philadelphia. The Fellows included Dr. Ralph W. Trimmer, Chicago; Dr. William W. Cadbury, Moorestown, N. J.; Dr. Joseph C. Edwards, St. Louis, Mo.; Dr. J. Russell Elkinton, Philadelphia; Dr. John R. Paul, New Haven, Conn.; Dr. J. S. L. Browne, Montreal, Que.; Dr. Warfield T. Longcope, Baltimore, Md.; Dr. William S. Middleton, Madison, Wis.; Dr. Joseph M. Hayman, Jr., Cleveland, Ohio; Dr. Henry M. Thomas, Jr., Baltimore, Md.; and Dr. Edward B. Krumbhaar, Philadelphia.

Among guest speakers at the annual meeting of the Connecticut State Medical Society, which was held in Stratford May 1-3, were Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y., "Inflammatory Diseases of the Small Intestine"; Dr. Elmer L. Sevringhaus, F.A.C.P., Essex Fells, N. J., "Uses and Limitations of Endocrine Therapy"; and Dr. Irvine H. Page, F.A.C.P., Cleveland, Ohio, "Nature and Treatment of Hypertension." Dr. John C. Leonard, F.A.C.P., Hartford, presided at a symposium on "Arteriosclerosis and Aging."

Among the guest speakers at the annual meeting of the Oklahoma State Medical Association in Tulsa, May 21-23, were Dr. Elliott P. Joslin, M.A.C.P., Boston, Mass., Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Ill., Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., and Dr. Ernest E. Muirhead (Associate), Dallas, Tex.

Herbert T. Kelly, M.D., F.A.C.P., Philadelphia, Pa., spoke on "Principles of Psychosomatic Medicine in Ophthalmology" at the Annual Meeting of The Pennsylvania Academy of Ophthalmology and Otolaryngology which was held on May 4, 1951, in Wernersville, Pa.

Dr. Esmond R. Long, F.A.C.P., Philadelphia, Pa., Editor of the American Review of Tuberculosis, was one of the speakers at the 43rd annual meeting of the Wisconsin Anti-Tuberculosis Association, which was held May 7-8, in Milwaukee.

Dr. George E. Wakerlin, F.A.C.P., Professor of Physiology at the University of Illinois College of Medicine, spoke on "The Kidney and Hypertension" at the meeting of the American Urological Association in Chicago, May 21-24.

MAJOR GENERAL GEORGE E. ARMSTRONG TO BECOME SURGEON GENERAL OF THE U. S. ARMY

It has been announced that Major General George E. Armstrong will succeed Major General Raymond W. Bliss as Surgeon General of the U. S. Army on June 1, 1951. General Armstrong served as the Deputy Surgeon General and prior thereto was the Chief of Personnel.

General Armstrong's professional career has been primarily in surgery. During World War II he became active in management operations of the medical service and played a major rôle in training of medical enlisted men and officers. He served in the China-Burma-India Theater of Operations as well as in the China Theater.

At the annual meeting of the Illinois Tuberculosis Association in April, 1951, Dr. Fred M. Meixner, F.A.C.P., Peoria, Illinois, was awarded the Certificate for

Distinguished Service in the field of tuberculosis control. Dr. Meixner was also elected a member of the Board of Directors and of the Executive Committee, for life, of The Illinois Tuberculosis Association. He is also chairman of the Committee on Tuberculosis of The Illinois State Medical Society.

Dr. Andrew C. Ivy, F.A.C.P., Secretary of the National Society for Medical Research, has announced the election of Dr. William Henry Sebrell, Jr., F.A.C.P., Bethesda, Md., to the Board of Directors of the Society. Dr. Sebrell is Medical Director of the U. S. Public Health Service and Chief of the Division of Physiology, National Institutes of Health.

Dr. Samuel J. Prigal, F.A.C.P., Assistant Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, participated in the Symposium on Aerosol Therapy which was held June 1-2, in Turin, Italy, under the auspices of Minerva and Italian Medical Societies.

Truman C. Terrell, M.D., F.A.C.P., Fort Worth, Texas, has been chosen President-Elect of the Texas State Medical Association at its recent 84th Annual Convention at Galveston. Dr. Terrell had been chairman of the Board of Trustees of his State Society for the past five years.

Dr. Samuel A. Levine, F.A.C.P., Clinical Professor of Medicine of Harvard Medical School and member of the senior staff of the Peter Bent Brigham Hospital of Boston, Mass., served as Professor of Medicine "Pro Tem" at Georgetown University School of Medicine for one week, April 1-7, 1951. During this week Dr. Levine acted as Director of the educational activities of the Department of Medicine at Georgetown University Hospital and Georgetown University School of Medicine in place of Dr. Harold Jeghers, F.A.C.P., Professor of Medicine and Physician-in-Chief of Georgetown University Hospital. Most of the program during the week was devoted to informal ward rounds and small group teaching with attendance limited to the senior medical students and the house staff.

Several sessions were open to the medical profession. These included: A combined Medical-Surgical Conference at the Georgetown University Medical Division of Gallinger Municipal Hospital on the subject, "The Thyrocardiac," on April 3, 1951, at which time Dr. Samuel A. Levine and Dr. Robert J. Coffey, Professor of Surgery, Georgetown University School of Medicine, were discussors; Medical Grand Rounds at Georgetown University School of Medicine on Tuesday, April 3, at which Dr. Levine acted as the chairman; A Clinical Pathological Conference at Georgetown University School of Medicine on Friday, April 6, while on the same day Dr. Levine gave a formal lecture on the subject "Myth of Strict Bed Rest in the Treatment of Heart Disease."

The General Leonard Wood Medal "for distinguished contribution to Medicine and Humanity" was presented to Dr. Chester S. Keefer, F.A.C.P., Boston, Wade Professor of Medicine, Boston University School of Medicine, and College Governor for Massachusetts, by the Boston City Hospital Alumni Association at its annual meeting on April 28. The meeting was arranged in recognition of the tenth anniversary of Dr. Keefer's directorship of the Evans Memorial Department of Massachusetts Memorial Hospital. Previous recipients of the medal have been Dr. Elliott P. Joslin, M.A.C.P., and Dr. William B. Castle, F.A.C.P. Among the speakers at the scientific session was Dr. Maxwell Finland, F.A.C.P., Boston, "Influenza and

Pneumonia." Dr. Keefer's address was entitled "Some Advances in Therapeutic Research."

Dr. George E. Burch, F.A.C.P., Professor of Medicine and Chairman of the Department, Tulane University School of Medicine, delivered the first George E. Fahr Lecture at the University of Minnesota on May 8. This lectureship is financed through a gift which former students of Dr. Fahr have presented to the Minnesota Medical School Foundation. Dr. Burch also participated in a continuation course in electrocardiography presented at the Center for Continuation Study May 7-11.

Among the speakers at the annual meeting of the Arkansas Academy of General Practice, which was held in Little Rock April 22, was Dr. Walter C. Alvarez, F.A.C.P., Chicago, Ill., whose subject was "The Future of GP."

Dr. Leonard A. Scheele, F.A.C.P., College Governor for the U. S. Public Health Service, was elected President of the World Health Assembly at the fourth annual assembly held in Geneva, Switzerland, on May 7.

Among the guest speakers at the recent meeting of the Medical Association of the State of Alabama which was held in Mobile, April 9-21, was Dr. Thomas A. Johnson, F.A.C.P., Philadelphia, Pa., who spoke on "Diagnosis and Management of Pancreatic Lesions."

Dr. Francis M. Pottenger, Jr., F.A.C.P., Monrovia, Calif., was appointed Secretary of the newly established Medical Commission on Environmental Contaminants, which was established by the Supervisors of Los Angeles County, acting on the recommendations of the Los Angeles County Medical Association. Its purpose is to conduct research on the effects of smog on health in the area.

Dr. Irving S. Wright, F.A.C.P., newly elected College Governor for Eastern New York, delivered the Abner Wellborn Calhoun Lecture at the annual meeting of the Medical Association of Georgia, held in Augusta, April 17-20. His topic was "Neurovascular Syndromes of the Shoulder Girdle Including Hyperabduction Syndrome."

Among the out-of-town speakers on the program of the annual session of the Missouri State Medical Association, which was held in Kansas City April 22-25, were Dr. Edward F. Rosenberg, F.A.C.P., Chicago, Ill., "Arthritis"; Dr. George E. Burch, F.A.C.P., New Orleans, La., "Use of Diuretics in Congestive Heart Failure"; and Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., "Sarcoidosis."

Dr. I. Arthur Mirsky, F.A.C.P., was recently appointed Professor of Clinical Science and Chairman of the Department of Clinical Science as well as Professor of Research Psychiatry at the University of Pittsburgh School of Medicine.

Dr. Ferdinand C. Helwig, F.A.C.P., Clinical Professor of Pathology and Oncology at the University of Kansas School of Medicine, served as moderator at a seminar on gynecologic pathology at a joint meeting of the Missouri Society of Pathologists and the South Central Region of the College of American Pathologists which was held April 21-22, in Kansas City.

Among the visiting speakers at a meeting of the Missouri Chapter of the American College of Chest Physicians which was held in Kansas City, April 22, were Dr. Andrew L. Banyai, F.A.C.P., Milwaukee, Wis., "Therapeutic Potentialities of Artificial Pneumoperitoneum" and Dr. Corrin H. Hodgson, F.A.C.P., Rochester, Minn., "Diagnosis and Management of Circumscribed Lesions of the Lungs."

Dr. Karl V. Kitzmiller, F.A.C.P., Cincinnati, Ohio, was recently promoted to Medical Director of the Ethyl Corporation. He has been with the Medical Department of the Ethyl Corporation since 1926.

Among the speakers at the third annual meeting of the Oklahoma Academy of General Practice, which was held in Enid, April 16-17, were Dr. William H. Gordon, F.A.C.P., Lubbock, Tex., and Dr. Edward C. Reifenstein, Jr., F.A.C.P., Oklahoma City, Okla.

Dr. George W. Thorn, F.A.C.P., Boston, Mass., spoke on "Mechanism of Action of ACTH and Cortisone" at the meeting of the American Association of Pathologists and Bacteriologists, held in Cleveland, Ohio, April 26-28.

Dr. Herbert R. Edwards, F.A.C.P., Executive Director of the New York Tuberculosis and Health Association, was the speaker for the anniversary luncheon which was part of a celebration marking fifty years' work in tuberculosis and public health by the Ohio Tuberculosis and Health Association, held May 16, in Cincinnati, Ohio.

Dr. Hobart A. Reimann, F.A.C.P., Philadelphia, Pa., delivered the Charles V. Chapin Oration during the annual meeting of the Rhode Island Medical Society, which was held in Providence, May 9-10. Dr. Reimann's topic was "Periodic Disease."

Dr. Edmund L. Keeney, F.A.C.P., San Diego, Calif., was one of the guest speakers at the meeting of the Arizona State Medical Association which was held in Tucson, April 29-30. Dr. Keeney's subject was "Medical Fungi, the Infections and the Allergies That They Provoke."

Dr. Edwin P. Peterson, F.A.C.P., Boise, was recently reappointed a member of the Idaho State Board of Eugenics.

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., spoke on "Treatment of Anemias" at the annual session of the California State Medical Association, held May 13-16 in Los Angeles.

Among the guest speakers at the annual session of the New Mexico Medical Society, held in Sante Fe, May 3-5, were Dr. George C. Griffith, F.A.C.P., Professor of Medicine, University of Southern California School of Medicine, Los Angeles, and Dr. Howard B. Sprague, F.A.C.P., Brookline, Mass., President of the American Heart Association.

Dr. Leo J. Wade (Associate), New York, N. Y., was recently appointed Medical Director of the Esso Standard Oil Company.

Dr. Karl Muschenheim, F.A.C.P., Attending Physician at the New York Hospital and Associate Professor of Clinical Medicine at Cornell University Medical College, was recently appointed Chairman of the Tuberculosis Committee of the New York Tuberculosis and Health Association.

CORRECTION

On page 840 of the March, 1951, issue of the ANNALS OF INTERNAL MEDICINE appeared an inaccurate statement that Dr. John Lansbury, F.A.C.P., Philadelphia, Pa., had been promoted from Clinical Professor to Professor of Medicine at Temple University School of Medicine. This note should have stated that Dr. Lansbury was promoted from Associate Professor to Clinical Professor of Medicine.

OBITUARIES

DR. HERBERT CHARLES MOFFITT

Herbert Charles Moffitt, B.S., M.D., LL.D., D.Sc., Clinical Professor of Medicine, Emeritus, at the University of California School of Medicine and one of the outstanding physicians of the country, died at the University of California Hospital, San Francisco, February 5, 1951.

Dr. Moffitt was born in San Francisco, December 9, 1867. He received his B.S. degree from the University of California in 1889. At his graduation he was designated Class Medalist, an award given for the highest record in scholarship and leadership in undergraduate years. He received his Medical Degree from Harvard Medical School in 1894. He interned at the Massachusetts General Hospital. Thereafter he followed postgraduate studies in Paris, Munich, Berlin and Vienna.

He returned to his native San Francisco and began the practice of medicine in 1898. A year later he was appointed Lecturer in the Principles and Practice of Medicine at the University of California School of Medicine. In 1900 he became Professor of Principles and Practice of Medicine at the same institution. Thus began one of the most distinguished medical careers in the West and a lifelong association with the medical school, to the advancement of which he contributed in great measure over a period of half a century. He soon attained recognition for his extraordinary abilities as administrator, teacher, educator and clinician. He served as Dean and Professor of Medicine of the University of California School of Medicine from 1912 to 1918. During this period he selected and induced a group of outstanding young scientists to join the medical school faculty. These later attained eminence in their respective fields and brought distinction to the medical school. Among them were Drs. Karl F. Meyer, Herbert T. Evans, William Palmer Lucas and George H. Whipple. He was largely responsible for inaugurating a program of full time teaching and research at the medical school. Although engaged in a busy practice, Dr. Moffitt kept alive his unflagging interest in research. He participated in some of the original experimental work in the treatment of pernicious anemia with liver. He made significant contributions to the study of peptic ulcer and in collaboration with Dr. William Ophuls established the mycotic nature of "Valley Fever" in California (coccidioidomycosis). During World War I he served in the Medical Corps, U. S. Army, as a Major. On his return he became Clinical Professor of Medicine at the University of California School of Medicine and Chairman of the Department of Medicine. It was largely through his individual efforts that funds were obtained for the construction of the present University of California Hospital which was completed in 1917. He was active as Clinical Professor of Medicine until his retirement in 1937 when he became Clinical Professor of Medicine, Emeritus.

He served on the Advisory Board and the Board of Trustees of the George Williams Hooper Foundation for Medical Research. In 1915-1916 he was the fourth Vice President of the American Medical Association. He was a member of the Association of American Physicians, of which he was President in 1922, a member of the Association for the Study of Internal Secretions, a Diplomate of the American Board of Internal Medicine, and a Past President of the San Francisco Medical Society. He was elected a Fellow of the American College of Physicians in 1932. He received his LL.D. from the University of California in 1919 and his D.Sc. from Harvard University in 1921. He was Consulting Physician, and at one time Physician-in-Chief, at the University of California Hospital.

Despite declining health and retirement from active medical pursuits, his interest never waned nor did he fail to keep abreast of medical progress. During World War II he was active in putting an effective nutrition program in San Francisco Bay

area shipyards and industrial plants. In June, 1950, in recognition of his contributions to the University of California School of Medicine, he was honored by the University when it was announced that the new 500-bed teaching hospital, now under construction in San Francisco, had been named for him.

Known to his students and colleagues alike as "The Chief," over the years he earned the admiration, affection and reverence of all who came within his influence. Dr. Moffitt possessed in extraordinary measure and in fine proportion a combination of attributes of mind, character and personality that made him preëminent above all as a teacher and a clinician. He had a brilliant, alert inquiring mind and an intellectual restlessness in the pursuit of knowledge that marked him as a lifelong scholar. In his approach to problems he "saw things steadily and saw them whole" but he never overlooked for a moment their minute component details. His memory was phenomenally retentive and accurate and his perception almost intuitively swift. He had an incisive wit and a gift of terse and vivid expression which made his comments memorable. To all who had the privilege of observing him it seemed as though all his long and varied experience was constantly mobilized and readily applicable to any current problem that confronted him. He was an able, resourceful and considerate consultant. His energy was incredible and he never wasted time or opportunity to enrich and cultivate his great natural gifts. He was an inspiring leader and, by example, evoked the best efforts of those about him. His influence upon generations of medical students and physicians in the West is incalculable. He was never indifferent to the many issues that inevitably arose, not only in his more familiar medical circles, but in his community and in the country. He was quick to speak out emphatically on such matters and to give effective support to any cause he considered worthy. Recognition, success and honors failed to breach his self-effacing manner and disarming modesty. Impatient of idle intrusion, he was never too pressed to inquire, out of genuine interest, about the personal interests and problems of others or to confer, unobtrusively, innumerable, "nameless, unremembered acts of kindness." He was indeed one of the choice spirits in American Medicine.

The Herbert C. Moffitt Memorial Hospital is a fitting tribute to the man who played such a dominant part in the development and advancement of the University of California School of Medicine. However, his greatest tribute is his abiding influence upon successive generations of students and physicians in the West and throughout the country, who regard him as their pattern and their ideal, of a great and beloved physician.

DWIGHT L. WILBUR, M.D., F.A.C.P.,
Governor for Northern California

DR. RICHARD H. M. BAYLEY

Richard Hugh McDowell Bayley, B.S., M.D., F.A.C.P., Lafayette, Ind., died suddenly at his home, January 18, 1951, of coronary thrombosis. He was born in 1891 in Battle Creek, Mich., and had his preliminary schooling at Marcellus, Mich.

He was graduated from the University of Michigan in 1915 with the B.S. degree and received his M.D. from the University of Michigan Medical School in 1920. He served an internship at St. Elizabeth Hospital, Lafayette, Ind., 1920-1921, following which he had resident training at the Wm. H. Maybury Sanatorium in Northville, Mich., and took some postgraduate work at the University of Michigan.

Dr. Bayley became associated with the Arnett-Crockett Clinic, Lafayette, Ind., in 1923, and was in charge of the Department of Internal Medicine in the clinic until his death. He was a member of the staffs of St. Elizabeth and Lafayette Home Hospitals for many years. He was a member and Past President of the Tippecanoe County Medical Society, a Fellow of the American Medical Association and a member

of the American Diabetic Association. He had been a Fellow of the American College of Physicians since 1931.

Probably no one attended the meetings of the College more faithfully than he; he had missed but four Annual Sessions since his election. To his many friends and patients, and to his many confreres in medicine his death came as a great shock. His wise counsel and sympathetic understanding will be greatly missed.

JAMES O. RITCHEY, M.D., F.A.C.P.,
Governor for Indiana

DR. ROBERT NICHOLAS BRAMHALL

Robert Nicholas Bramhall, B.S., M.D., of Fair Oaks, Calif., an Associate in the College, was born in Abingdon, Va., in 1878. He was a graduate of Shurtleff College in 1899 and of the Northwestern University Medical School in 1902. He served in World War I as a member of the Medical Corps, U. S. Army, following which he received further training at the Henry Ford Hospital in Detroit under the direction of Dr. Frank Sladen, Chief of the Medical Service. Dr. Bramhall came to Sacramento to practice in 1919 and remained there until his retirement in 1940. He was at one time Internist and Chief of Staff of the Sutter General Hospital. He was a Past President and former Secretary of the California Northern District Medical Society and a Director of the Sacramento Society for Medical Improvement. He died of a cerebral hemorrhage December 16, 1950.

DWIGHT L. WILBUR, M.D., F.A.C.P.,
Governor for Northern California

DR. IVAN HEKIMIAN

Ivan Hekimian, A.B., M.D., F.A.C.P., was born in Russia, August 22, 1897. He was a graduate of the University of Buffalo School of Medicine, and received his M.D. in 1927.

Following his internship and residency at the Buffalo General Hospital, Dr. Hekimian became Clinical Assistant and later Attending Physician at that institution. He was also a member of the faculty of the University of Buffalo School of Medicine, and advanced from Instructor in Medicine to Assistant Professor of Medicine.

During World War I, Dr. Hekimian served in the Intelligence Corps, British Expeditionary Force. He was a Fellow of the American Medical Association and a member of his state and county medical societies. He was also a member of the Buffalo Academy of Medicine and the American Diabetes Association, and was elected a Fellow of the American College of Physicians in 1934. Dr. Hekimian died January 23, 1951, of coronary thrombosis.

EDWARD C. REIFENSTEIN, M.D., F.A.C.P.,
Governor for Western New York

DR. HORACE RUTHERFORD LIVENGOOD

Horace Rutherford Livengood, M.D., F.A.C.P., of Elizabeth, N. J., died at the Harkness Pavilion, Columbia-Presbyterian Medical Center, New York, N. Y., on December 31, 1950. He was born in Salisbury, Pa., December 4, 1876.

He was educated at Pingry School, Elizabeth, N. J., attended the Columbia University School of Mines and received his M.D. degree from Columbia University College of Physicians and Surgeons in 1899. He did postgraduate work in Paris and Berlin in 1904.

Dr. Livengood manifested a great interest in internal medicine and cardiology during all of his scientific life and made many contributions to the literature. He

was Senior Attending Physician at the Elizabeth General Hospital since he completed his residency there in 1901 and, additionally, Consulting Physician at the Alexian Brothers Hospital and St. Elizabeth Hospital in Elizabeth, N. J.

During World War I he served as a Captain in the Medical Corps, U. S. Army, and was Chairman of the Union County Medical Board No. 9, Elizabeth, N. J., during World War II.

He was decidedly civic-minded and for many years served as Commissioner of the Elizabeth Board of Health. He was very fond of travel and visited many parts of Europe including England, Scandinavia, France, Germany, Russia, Italy, the West Indies and all parts of the United States.

He was Past President of the Union County Medical Society of New Jersey, a Life Member of the American College of Physicians and a Diplomate of the American Board of Internal Medicine.

Dr. Livengood's memory will live in the hearts of his family, his friends and his patients. He lived a full, active, energetic, untiring life. The medical profession in Elizabeth, N. J., has lost a colleague of outstanding ability and great personal charm. We shall miss him greatly.

FREDERICK HNAT, M.D., F.A.C.P.

DR. ALBERT E. LUCKHARDT

Albert E. Luckhardt, A.B., B.S., M.D., F.A.C.P., was born in Chicago, Ill., on July 29, 1878. He received his A.B. degree in 1895 from Conception College (Missouri). He studied medicine in the great German universities and received his M.D. degree in 1901 from the University of Freiburg. Dr. Luckhardt was an accomplished pianist and even during his medical school days in Germany was a serious student of the piano.

Dr. Luckhardt was a busy practitioner of medicine for nearly fifty years in Chicago, but he always kept up his study of piano music and played with great skill for his devoted family, friends and patients. He was active in the affairs of the German Medical Society in Chicago and throughout his life he played the piano to the great delight of the members of this organization.

Dr. Luckhardt was truly a cultured gentleman, scholar and physician and the members of his family, his friends and his patients were always devoted to him. His patients usually became his friends. He had the kindness, the sympathy and the culture of a great doctor.

At various times throughout his career Dr. Luckhardt took postgraduate courses in medicine in Germany and in this country. In Chicago he served on the staffs of the Grant and St. Elizabeth Hospitals. For many years he was Assistant Professor of Clinical Medicine at Loyola University School of Medicine, and was a Diplomate of the American Board of Internal Medicine.

Dr. Luckhardt was elected a member of the American Congress on Internal Medicine in 1924 and later became an Associate in the American College of Physicians. He died on January 6, 1951, of carcinomatosis.

Dr. Luckhardt is survived by his wife, Ruby, five children, eight grandchildren and his brother, Dr. Arno B. Luckhardt, William Beaumont Distinguished Service Professor of Physiology at the University of Chicago School of Medicine.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

ABSTRACTED MINUTES OF THE JOINT EXECUTIVE SESSION OF THE BOARD OF REGENTS AND BOARD OF GOVERNORS

ST. LOUIS, Mo.

APRIL 8, 1951

The Annual Joint Meeting of the Board of Regents and the Board of Governors of the American College of Physicians was held at the Kiel Auditorium, St. Louis, Mo., at 2:00 p.m., Sunday, April 8, 1951, with President William S. Middleton presiding. Those present were:

Officers and Regents: William S. Middleton, *President*; Maurice C. Pincoffs, *President-Elect*; Ernest H. Falconer, *First Vice President*; Arthur T. Henderson, *Third Vice President*; William D. Stroud, *Treasurer*; George Morris Piersol, *Secretary-General*; Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, Wallace M. Yater, Edward L. Bortz, Harold H. Jones, William S. McCann, T. Grier Miller, Charles F. Moffatt, A. B. Brower, Alex. M. Burgess, Reginald Fitz, George H. Lathrope, Cyrus C. Sturgis, and Walter L. Palmer, *Chairman, Board of Governors*.

Governors:

Leslie R. Kober, Phoenix	ARIZONA
Lemuel C. McGee, Wilmington	DELAWARE
William C. Blake, Tampa	FLORIDA
Carter Smith, Atlanta	GEORGIA
Samuel M. Poindexter, Boise	IDAHO
J. Murray Kinsman, Louisville	KENTUCKY
Richard S. Hawkes, Portland	MAINE
Wetherbee Fort, Baltimore	MARYLAND
John G. Archer, Greenville	MISSISSIPPI
Harold W. Gregg, Butte	MONTANA and WYOMING
Walter I. Werner, Albuquerque	NEW MEXICO
Charles A. Doan, Columbus	OHIO
Howard P. Lewis, Portland	OREGON
David W. Carter, Jr., Dallas	TEXAS
Karver L. Puestow, Madison	WISCONSIN
*Rurico S. Diaz-Rivera, San Juan	PUERTO RICO
*H. Archibald DesBrisay, Vancouver	ALBERTA and BRITISH COLUMBIA
Charles H. A. Walton, Winnipeg	MANITOBA and SASKATCHEWAN
Leland Hawkins, Los Angeles	CALIFORNIA (Southern)
Ward Darley, Denver	COLORADO
*J. Alfred Wilson, Meriden	CONNECTICUT
John Minor, Washington	DISTRICT OF COLUMBIA
Charles H. Drenckhahn, Urbana	ILLINOIS (Southern)
James O. Ritchey, Indianapolis	INDIANA
William C. Menninger, Topeka	KANSAS
*Walter S. Burrage, Boston	MASSACHUSETTS
Joseph D. McCarthy, Omaha	NEBRASKA
Edward C. Reifenstein, Sr., Syracuse	NEW YORK (Western)
Wann Langston, Oklahoma City	OKLAHOMA
Thomas M. McMillan, Philadelphia	PENNSYLVANIA (Eastern)

* Alternate.

Charles W. Morton, Pittsburgh	PENNSYLVANIA (Western)
Charles F. Morsman, Hot Springs	SOUTH DAKOTA
William C. Chaney, Memphis	TENNESSEE
Fuller B. Bailey, Salt Lake City	UTAH
Herbert K. Detweiler, Toronto	ONTARIO
*C. D. Briscoe, Panama	REPUBLIC OF PANAMA and the CANAL ZONE
Arless A. Blair, Fort Smith	ARKANSAS
Dwight L. Wilbur, San Francisco	CALIFORNIA (Northern)
Benjamin F. Wolverton, Cedar Rapids	IOWA
Thomas Findley, New Orleans	LOUISIANA
Wesley W. Spink, Minneapolis	MINNESOTA
Ralph A. Kinsella, St. Louis	MISSOURI
Harry T. French, Hanover	NEW HAMPSHIRE
Edward C. Klein, Jr., Newark	NEW JERSEY
*Paul F. Whitaker, Kinston	NORTH CAROLINA
*L. H. Fredricks, Bismarck	NORTH DAKOTA
*L. I. Kramer, Providence	RHODE ISLAND
Robert Wilson, Jr., Charleston	SOUTH CAROLINA
Ellsworth L. Amidon, Burlington	VERMONT
Charles M. Caravati, Richmond	VIRGINIA
*Charles E. Watts, Seattle	WASHINGTON
Paul H. Revercomb, Charleston	WEST VIRGINIA
*Norman S. Skinner, St. John, N. B.	MARITIME PROVINCES
Walter de M. Sriver, Montreal	QUEBEC
Harry G. Armstrong	UNITED STATES AIR FORCE
*Paul S. Fancher	UNITED STATES ARMY
*Otis L. Anderson	UNITED STATES PUBLIC HEALTH SERVICE
*Ernest R. Gentry	UNITED STATES VETERANS AD- MINISTRATION

PRESIDENT WILLIAM S. MIDDLETON: "We shall have reading of communications by the Secretary."

SECRETARY EDWARD R. LOVELAND: "Our first communication is from Dr. Edgar Hull, Second Vice President of the College, who is absent because of a teaching assignment in Bologna, Italy, this being his first absence for the past fifteen years."

"Our second communication is from Dr. William J. Kerr, official representative of the American College of Physicians at the First International Congress of Internal Medicine in Paris (read letter in full)."

"The third communication is from Dr. Elbert L. Persons, College Governor for North Carolina, who was appointed by President Middleton as the official representative of the College at the inauguration of Dr. Harold W. Tribble as President of Wake Forest College."

"The fourth communication is a telegram from the Oregon State Medical Society, through Dr. R. F. Miller, Secretary, to wit:

'The Council of the Oregon State Medical Society, at its meeting on November 11, 1950, unanimously voted to urge the American College of Surgeons to continue hospital standardization program until the American Medical Association and other representative organizations of the medical profession can join with the College of Physicians in financing and establishing a joint standardization program.'

* Alternate.

"The fifth communication is from President Middleton, revealing his having taken the responsibility of informing the President of the Second International Gerontological Congress that the American College of Physicians will be perfectly willing to be listed as a coöperating association in connection with that Congress at St. Louis, Mo., September 9-14, 1951.

"The sixth communication is from the Editor of the *ANNALS OF INTERNAL MEDICINE*, in regard to complimentary subscriptions through CARE to institutions in certain foreign countries. A year ago the Board of Regents authorized eleven or more complimentary subscriptions to be distributed to medical institutions, chiefly libraries in Czechoslovakia, Austria, Germany, Finland, Greece, Italy and Korea. The anniversary of these complimentary subscriptions was reached on December 31, 1950, and by reason of necessity, the one to Korea was cancelled, and the balance were reserved for advice from the Board of Regents. The action of the Board in authorizing these complimentary subscriptions had no doubt been motivated by the desire to have the College participate in a mixed philanthropic and propagative endeavor."

On the recommendation by Dr. Maurice C. Pincoffs, a resolution was unanimously adopted, providing for the continuation of the remaining complimentary subscriptions through CARE.

SECRETARY LOVELAND (continuing): "The seventh communication is from Dr. Charles A. R. Connor, Medical Director of the American Heart Association, calling to our attention that the College is entitled to two representatives on the American Council on Rheumatic Fever, and pointing out that heretofore Dr. William D. Stroud has been the sole representative of the College."

(Action was deferred until a later meeting of the Board of Regents.)

SECRETARY LOVELAND (continuing): "The last communication is from Dr. William B. Bean, of the State University of Iowa College of Medicine, taking issue with the rules of the College with respect to restriction of attendance by hospital residents and others in that category, regardless of the intent of the College to restrict attendance only within physical accommodations for members. The correspondent had felt that every encouragement for graduate training should be afforded to hospital residents throughout the country and that they should be charged no attendance fee. Dr. Bean was informed that the regulations governing non-member attendance at the Annual Sessions of the College had been adopted only because facilities in most cities are inadequate to take care of members at Panel Discussions, Clinics and other program features. Dr. Bean had been asked to suggest a solution to the problem, and Governor Benjamin F. Wolverton, of Iowa, had likewise been consulted."

DR. BENJAMIN F. WOLVERTON: "It has long been a policy of the College to give all possible encouragement to young men taking postgraduate training in Internal Medicine. Many of these will be future members of the College. For a great many years residents and internes in hospitals in cities in which the Annual Sessions are held have been admitted to meetings without restriction or fee. What Dr. Bean would like to see done is to extend the geographic limitation on such registration to include the country at large. In my opinion not enough individuals would be affected to create any marked increase in the total attendance, and I should like to see the Board of Regents change the present regulations."

DR. REGINALD FITZ: "At our last Annual Session in Boston we had experience with this situation. I can only say that our meeting halls were so filled that if many more had been allowed to attend without being properly qualified according to the rules, there would have been more complaints and dissatisfaction. It is a serious problem, because Fellows of the College themselves do not like to be crowded out of the meetings."

DR. WOLVERTON: "The increase in attendance at the Annual Sessions, aside from the fact that the College membership has grown greatly in recent years, is due chiefly to physicians in practice in the general area of the meeting who look upon it

as a very good and very inexpensive postgraduate course. That is the group that needs to be limited, rather than hospital residents and internes. Every one knows these young men are pursuing their graduate work under strenuous financial circumstances, and that is the kernel of Dr. Bean's objection. It imposes a financial barrier on these young men in their attendance at the Annual Sessions."

PRESIDENT MIDDLETON: "I shall ask that a special article of business, both for the Board of Governors and for the Board of Regents, shall be scheduled at later meetings of these Boards.

"Now that the attendance at this meeting is presumably complete, we will proceed with the reading of abbreviated Minutes of the last meeting of the Board of Regents."

The Secretary read an abstract of the Minutes of the Board of Regents held in Philadelphia, Pa., November 12, 1950, said Minutes being unanimously approved by resolution.

PRESIDENT MIDDLETON: "Next is the report of the Secretary-General, Dr. George Morris Piersol."

DR. GEORGE MORRIS PIERSOL: "Mr. President, Regents and Governors, since the last meeting of the Board of Regents, we have lost by death 32 Fellows and 3 Associates, to wit:

Fellows

Chesley, Faris Franklin	Chicago, Ill.	September 12, 1950
*Coffen, T. Homer	Portland, Ore.	January 9, 1951
Conner, Lewis Atterbury	New York, N. Y.	December 3, 1950
Craig, Charles F.	M.C., U. S. Army	December 9, 1950
Crane, Langdon Teachout	Bloomfield Hills, Mich.	January 3, 1951
Dumphy, John J.	Worcester, Mass.	December 19, 1950
Gage, John G.	Arcadia, Calif.	November 18, 1950
Goldsmith, Leon A.	Portland, Ore.	November 2, 1950
Gordon, Douglas Meharg	Ponca City, Okla.	October 28, 1950
Hanzlik, Paul John	San Francisco, Calif.	February 1, 1951
Jackson, John Bert	Kalamazoo, Mich.	November 3, 1950
Jones, Harry L.	Kansas City, Mo.	December 13, 1950
Lippincott, Leon S., Sr.	Daytona Beach, Fla.	November 25, 1950
Livengood, Horace R.	Elizabeth, N. J.	December 30, 1950
Mabey, J. Corwin	Montclair, N. J.	December 17, 1950
Mariette, Ernest Sidney	Wayzata, Minn.	October 29, 1950
Moffitt, Herbert C., Sr.	San Francisco, Calif.	February 5, 1951
Patterson, Robert U.	M.C., U. S. Army	December 6, 1950
Peterson, Edwin	M.C., U. S. Navy	December 2, 1950
Pratt, George Peyton	Omaha, Nebr.	December 19, 1950
Reye, H. A., Sr.	Detroit, Mich.	December 6, 1950
Rooney, James Francis	Albany, N. Y.	February 8, 1951
Shanno, Ralph Leopold	Forty Fort, Pa.	February 14, 1951
Smart, Elliott Plummer	Murphys, Calif.	October 13, 1950
Smith, Walter Fox	Watertown, N. Y.	February 3, 1951
Sweeney, John A.	Philadelphia, Pa.	February 14, 1951
**Trask, John William	Pittsfield, Mass.	January 6, 1951
Walker, Thomas F., Sr.	Great Falls, Mont.	October 22, 1950
White, Franklin Warren	Chestnut Hill, Mass.	December 19, 1950
Winnett, Edwin Basom	Des Moines, Iowa	December 8, 1950
Wolfe, Edward I.	Forty Fort, Pa.	February 16, 1951
Yoder, Paul Allison	Winston-Salem, N. C.	February 12, 1951

* Former Governor, Regent and Vice President.

** Phillips' Medalist.

Associates

Bramhall, Robert Nicholas	Fair Oaks, Calif.	December 16, 1950
Eberly, Karl Coulson, Sr.	Fort Wayne, Ind.	January 8, 1951
Williams, David R.	Girard, Ohio	October 15, 1950"

At the suggestion of President Middleton, members arose for a moment of silent tribute to those deceased.

DR. PIERSON (continuing): "Also, since the last meeting of the Board of Regents, 52 additional Fellows have become Life Members, making a grand total of 927, of whom 90 are now deceased, leaving a balance of 837. The new Life Members, listed in the order of their subscription, are as follows:

Samuel Simkins	Philadelphia, Pa.
Sidney Davidson	Lake Worth, Fla.
Leslie G. Kindschi	Monroe, Wis.
J. W. McMeans	Florence, S. C.
Joseph Levy	New Rochelle, N. Y.
Frank Lamberta	Jamaica, N. Y.
William Taliaferro Thompson, Jr. ...	Richmond, Va.
George N. Thompson	Los Angeles, Calif.
John Eiman	Abington, Pa.
Kurt Berliner	New York, N. Y.
William E. Hill	Naugatuck, Conn.
Irving E. Steck	Chicago, Ill.
Cecil C. Dustin	Rochester, N. H.
Orville E. Egbert	El Paso, Tex.
Joseph S. Hiatt, Jr.	McCain, N. C.
Matthew T. Moore	Philadelphia, Pa.
William S. Norton, II	New York, N. Y.
Harold A. Rosenbaum	Chicago, Ill.
Francis J. Scully	Hot Springs National Park, Ark.
William B. Terhune	New Canaan, Conn.
Albert VanderKloot	Chicago, Ill.
Harry F. Wechsler	New York, N. Y.
Ruth Walker Wilson	Beaver, Pa.
Forrest R. Ostrander	South Mountain, Pa.
Edgar S. Henry	Sewickley, Pa.
Emilie Vielt Rundlett	Jersey City, N. J.
Eugene S. Talbot	Chicago, Ill.
Herbert E. Christman	Lakewood, Ohio
Frank P. Goodwin	Jamestown, N. Y.
Ralph Waldo Mendelson	Albuquerque, N. M.
William Calvert Chaney	Memphis, Tenn.
Robert Cooke Kimbrough, Jr.	Knoxville, Tenn.
Sidney Adler	Detroit, Mich.
Irving I. Edgar	Detroit, Mich.
George H. Houck	Palo Alto, Calif.
William H. Smith	Baltimore, Md.
Robert W. Langley	Los Angeles, Calif.
John O. Westwater	Los Angeles, Calif.
Howard M. Sheaff	Oak Park, Ill.
Edward Randall, Jr.	Galveston, Tex.
George W. Lynch	Boston, Mass.

J. David Roger	Ottawa, Ont., Canada
John A. Schindler	Monroe, Wis.
Maxwell L. Gelfand	New York, N. Y.
Frank A. Marshall	Weehawken, N. J.
John B. Levan	Reading, Pa.
Francis L. Foran	Chicago, Ill.
Emile Gordon Stoloff	New York, N. Y.
Chauncey Angus McKinlay	Minneapolis, Minn.
Carll S. Mundy	Toledo, Ohio
J. Burns Amberson	New York, N. Y.
Arthur A. Holbrook	Milwaukee, Wis."

On motion made, seconded and unanimously carried, the report was accepted.

PRESIDENT MIDDLETON: "Next on our agenda is the presentation of memorials by the Chairman of that Committee, Dr. T. Grier Miller."

DR. T. GRIER MILLER: "Mr. President, Regents and Governors: it is proper to say that each of these memorials was prepared by a different member of the Committee:

DOCTOR ALLEN ARTHUR JONES

"Allen Arthur Jones died on June 19, 1950, following a long illness. He was 86 years of age, having been born in Prescott, Ont., Canada, in 1864. He received his M. D. degree in 1889 from the University of Buffalo School of Medicine, and interned at the Buffalo General Hospital. He had a long period of postgraduate studies, including work at the University of Buffalo and in Vienna, Berlin, Rome, Florence, Paris and London. For many years Dr. Jones was Professor of Medicine in the University of Buffalo School of Medicine and Consulting Physician to the Buffalo General and Millard Fillmore Hospitals. He was elected to Fellowship in this College in 1924 and served as Governor for Western New York, as a member of the Committee on Credentials and as Vice President.

"Dr. Jones was a kindly man and he personified the true physician. He was the trusted adviser and friend of many students, physicians and patients. A note from one of his confreres in Buffalo states, 'I used to go to Dr. Jones when I was so blue that it rubbed off on the side of the door and would come away with the thought that I was the most important citizen in town.'

"He was a well trained, professional gentleman of the old school who promptly took advantage of modern discoveries and left a lasting memory in his community."

DOCTOR FRANCISCO DE P. MIRANDA

"Francisco de P. Miranda died on April 28, 1950, at the age of 60. He was a Mexican, born in Puebla, a graduate of the Medical School of the National University of Mexico in 1914, and, for 17 years, had been a Fellow of this College, its Governor for Mexico since 1933.

"Dr. Miranda's chief medical interests were in endocrinology and nutrition, in which fields he pioneered in his country. He became a clinical professor of medicine in his alma mater in 1930, and later its first professor of endocrinology. He also was chief of a medical service in the General Hospital of Mexico and Consulting Endocrinologist and Nutritionist in the National Institute of Cardiology. He was largely responsible for the founding of the Institute of Nutrition in Mexico in 1943, and was its Director almost to the time of his death.

"In the early period of his medical career, which was during the Mexican Revolution, he participated in sanitary activities particularly with reference to outbreaks of

typhus fever in 1915 and 1918, later becoming chief sanitary officer in Matamoros and a representative of the Department of Health at various congresses. Then he became deeply concerned about the nutritional problems of his country, carrying this interest into his teaching and research. He published various papers on this and endocrinological subjects, and was a member of many medical organizations, including others than this College in the United States.

"Those who knew Dr. Miranda were impressed not only by his accomplishments in medicine, but also by his broad culture, his keen sense of humor and his human kindness. He will be greatly missed by his many friends in the College of Physicians, and his excellent services as one of its Governors will long be remembered."

DOCTOR WALTER WALKER PALMER

"Walter Walker Palmer died on October 28, 1950. He was 68 years old. In 1928, seven years after being appointed Professor of Medicine at Columbia University and Director of the Medical Service of the Presbyterian Hospital in New York, he became a Fellow of the American College of Physicians. He was one of the hardy perennials which were transplanted into our garden at 4200 Pine Street by that astute horticulturist, Dr. Charles F. Martin, who anticipated that such plants would flourish in new surroundings, and sooner or later, by their flowering, would add to our luster.

"Dr. Palmer's roots in the College took hold slowly, but as time advanced they grew deep and strong. Little by little all that Dr. Martin hoped of him came into fruition.

"Dr. Palmer served as Governor for Eastern New York, as Regent, as Second Vice President, as President-Elect and as President. In these several capacities he became a member of various of our Committees—the Committee on the Annals of Internal Medicine, the Executive Committee, the Committee on the Alfred Stengel Memorial. His interest, his loyalty and his leadership helped to shape the personality of the College during the years of its growing pains, and, as it came to maturity, added to its character and distinction. Whatever he was asked to do he accomplished with tact, good judgment and sound common sense.

"Those Officers, Regents and Governors who were associated with him will remember him with gratitude; as well as any Fellow could, he furthered the aims of the College by the manner in which he maintained, in the words of our Constitution, 'the dignity and the efficiency of Internal Medicine in its relationship to public welfare.'"

On motion seconded and regularly carried, the memorials were adopted, and the Secretary instructed to spread them on the Minutes of this meeting and to transmit copies to members of the families.

PRESIDENT MIDDLETON: "Next will be the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman."

DR. PIERSOL: "Mr. President and members of the Board of Regents and of the Board of Governors: since the last meeting of the Board of Regents, the Committee on Credentials has held two meetings, the first at Philadelphia, Pa., on March 11, 1951, at which all members of the Committee were present, and the second at St. Louis, Mo., on April 7, 1951, also with all members present, and with two observers from among the new Governors, namely, Dr. Charles H. Drenckhahn, Governor for Southern Illinois, and Dr. Paul H. Revercomb, Governor for West Virginia. The following is the Minutes of our meeting on March 11:

"Communications:

"(1) Full data were received concerning the new American Board of Nutrition, with a request for advice as to whether this Board will be recognized by the American College of Physicians with respect to certification of candidates for Fellowship.

"This is a newly organized Board not under the Advisory Board for Medical Specialties of the American Medical Association. It proposes to certify not only M.D.'s, but also Ph.D.'s. The Board's postgraduate medical requirements are not comparable to those of the American Board of Internal Medicine. The Committee on Credentials considers this new Board as filling a field not applicable to a medical specialty, and recommends non-recognition of the Board by the College, so far as certification of candidates for Fellowship is concerned.

"(2) A resolution, endorsed by thirty-eight members of the College from the State of Kentucky, decrying the more rigid criteria for election to Associateship and advancement to Fellowship, particularly with regard to minimal ages and the submission of publications, and recommending particularly that a candidate's professional ability shall be established more on the recommendations of Fellows who know him well and the record of his local activities."

The Committee directed the Secretary to acknowledge the resolution and covering letter, and to refer the contents to the special committee of the Board of Governors now studying this problem, that Committee consisting of Dr. Charles A. Doan, Chairman, Dr. Robert Wilson, Jr., and Dr. Dwight L. Wilbur.

"(3) A letter from Dr. William F. Ashe, F.A.C.P., concerning industrial physicians and their place in the College."

Discussion of the status of industrial physicians will appear in the minutes of the second meeting of the Committee on Credentials.

"(4) The Committee discussed the matter of the extension of the terms of Associates from civil life who are entering military service, and voted to recommend to the Board of Regents that the Associate term of any such civilian physician be extended after his release from active duty for a period commensurate with that which he served on military service. The Committee pointed out, however, that this does not, under present conditions, refer to Associates who are already in the regular Medical Corps of the military services. This recommendation is in keeping with the action taken by the Board of Regents during World War II."

PRESIDENT MIDDLETON: "What is the wish of this Board relative to adopting the recommendation of the Committee on Credentials with regard to extension of Associate terms of those called to active military duty?"

On motion by Dr. Reginald Fitz, seconded and regularly carried, the recommendation of the Committee was approved.

DR. PIERSOL (continuing): "The Committee on Credentials received some applications for extension of Associate terms."

After consideration of the situations in each individual case, the Committee recommended the extension of the terms of five Associates for periods of one to two years, due to illnesses which were of a somewhat extended nature. In the case of one Associate the Committee recommended no further extension because the application was not justified under regulations and provisions of the By-Laws.

On motion seconded and unanimously carried, the recommendations concerning extensions of Associate terms were approved.

DR. PIERSOL (continuing): "Dr. George H. Lathrope, a member of the Committee, introduced the recommendation that the notice to Associates of their eligibility to present their credentials for advancement to Fellowship be delayed until after their minimal three-year term has actually expired, rather than being sent to them a few months before the expiration of the minimal term, as has been done heretofore. He felt that several proposals for advancement to Fellowship are somewhat premature. The Committee agreed to his recommendation.

"A summary of the action of the Committee on candidates at the meeting on March 11, 1951, is as follows:

I. *Candidates for FELLOWSHIP:*

Recommended for Advancement	110	
Recommended for Direct Election	4	114
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Recommended for Election First to Associateship	2	
Deferred	44	
Rejected	3	
<hr/>		
TOTAL Fellow Candidates		163
<hr/>		

II. *Candidates for ASSOCIATESHIP:*

Recommended for Election	100	
*Proposed for Fellowship, but Recommended First for Election to Associateship	2	102
<hr/>		
Deferred	28	
Rejected	4	
<hr/>		
TOTAL Associate Candidates		132*
*Plus Fellowship Candidates Recommended for Associateship	2	
<hr/>		
		134
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"Before presenting the names of candidates recommended for election, we will proceed to the Minutes of the second meeting of the Committee on April 7, 1951, and submit a combined list of all candidates recommended for election.

"At the second meeting of the Committee, the presence of two observers from the Board of Governors was a great help and stimulus, and led us to feel that if more Governors had attended, some of these meetings might be a further mutually advantageous procedure.

"The Committee reopened a discussion of the matter of candidates following the specialty of industrial medicine. After a thorough discussion of the subject of passing on candidates from this specialty and reviewing past precedence, showing there had been since 1940 twelve advanced to Fellowship without certification and ten with certification, the Committee voted that all present Associates whose specialty is industrial medicine shall not be required to be certified by the American Board of Internal Medicine, or by other specialty boards, as a requirement for their advancement to Fellowship, it being tacitly agreed that their original election to Associateship was on that basis. It was further agreed that for the future, the Committee will not consider for Associateship any candidate in the field of industrial medicine who is not primarily engaged in clinical work in the field of Internal Medicine, or other specialty that has been accepted by the College, and that such candidate shall be required to demonstrate that he will have requisite requirements for eligibility to admission to the examinations of the American Board of Internal Medicine, or other acceptable Board. The Committee further suggested that two members of the Committee, Dr. George Morris Piersol and Dr. Lemuel C. McGee, shall confer with the Chairman of the American Board of Internal Medicine, in order to establish a better understanding of the status of such candidates and their admission to Board certification.

"At this second meeting of the Committee on Credentials, the following is a summary of action recommended on candidates to the Board of Regents:

I. *Candidates for FELLOWSHIP*

Recommended for Advancement	68
Recommended for Direct Election	1 69
<hr/>	
Recommended for Election First to Associateship	1
Deferred	18
Rejected	15

TOTAL Fellow Candidates 103

II. *Candidates for ASSOCIATESHIP*

Recommended for Election	53
* Proposed for Fellowship, but Recommended First for Election to Associateship	1 54
<hr/>	
Deferred	14
Rejected	5

TOTAL Associate Candidates 72

* Plus Fellowship Candidate Recommended for Associateship 1

73

"The Committee has combined the groups of recommended candidates for its two meetings, and has placed in your hands at this time the lists. The Committee moves the election of 183 candidates for Fellowship and of 156 candidates for Associateship, per the appended duplicated names." (The official list of elections to Fellowship and to Associateship was published in the May, 1951, issue of this journal.)

The motion was seconded and unanimously carried.

Dr. Piersol, continuing his report, called attention to the fact that the maximal Associate term of a group of 67 candidates had expired with that meeting. The group included not only a portion of the Associates who were elected five years previously, Spring, 1946, but also a certain number of Associates elected prior to that time but whose terms had been extended because of military duty during World War II. This group of Associates had either not presented adequate credentials for advancement to Fellowship or had not made any attempt to qualify. Their names were recorded in the minutes and they were automatically dropped from the Associate Roster in accordance with the regulations of the By-Laws of the College.

Upon motion, regularly seconded and unanimously carried, the report of the Committee on Credentials was approved as a whole.

PRESIDENT MIDDLETON: "The next article of business is the report of the Conference Committee on Graduate Training in Medicine by Dr. LeRoy H. Sloan."

DR. LEROY H. SLOAN: "Mr. President, the next meeting of the Conference Committee on Graduate Training in Medicine will be at the time of the meeting of the American Medical Association at Atlantic City in June. Since the last meeting a local Committee in Chicago has been coöperating with the American Board and the American Medical Association in the certification of hospitals. Questionable certifications of hospitals have been submitted to us and then returned to the American Medical Association's Council on Medical Education and Hospitals for further action. The Committee meeting in June will summarize the work of the entire year, and will possibly adopt somewhat more stringent and effective techniques in certification."

PRESIDENT MIDDLETON: "The next article of business is the report of the Committee on Fellowships and Awards, Dr. Cyrus C. Sturgis, Chairman."

DR. CYRUS C. STURGIS: "The Committee on Fellowships and Awards met at 10:00 a.m., April 8, 1951, in the Kiel Auditorium, St. Louis. Those present included Dr. T. Grier Miller, Dr. Walter L. Palmer, Dr. Maurice C. Pincoffs, Executive Secretary E. R. Loveland and the Chairman.

"The work of the Latin-American Fellows was reviewed. There are now 16 Latin-American Fellows in this country—3 in Cardiology; 5 in Gastro-enterology; 1 in Hematology; 3 in General Medicine; 3 in Pathology; and 2 in Physiology. One Latin-American Fellow, Dr. Luiz Carlos de Barros, of Brazil, for personal reasons, gave up his fellowship and returned to Brazil on March 8, 1951. 5 of the Fellows are in Boston; 3 in Minnesota; 3 in Michigan; 2 at University of Pennsylvania; 2 in New York City, and 1 in Chicago. Ten Latin-American Fellows will attend the 32nd Annual Session of the American College of Physicians in St. Louis.

"It was agreed that the Committee on Fellowships and Awards should:

- (1) Meet in Ann Arbor, Mich., some time in June, 1951. This is to permit more time for the selection of new Fellows, and there will be at least 13 for consideration, so that they may report for their fellowships by September 1. It would also be advantageous, as it makes more certain a full attendance of the Committee before summer vacations begin.
- (2) It was voted to select the candidate for the Phillips' Award and also the Bruce Award at the June meeting for submission to the Executive Committee of the College. These candidates, thus selected early, are more likely to accept and thereby be given more time for the preparation of their papers to be presented for the next Annual Session of the College.
- (3) It was decided to recommend to the Regents that the recipient of the Phillips' Award have all his expenses paid to the meeting and in addition receive an honorarium of \$250.00 and the Phillips' Medal.
- (4) That the honorarium for the Bruce Award be \$400.00, which is approximately the amount yielded by the endowment left by Dr. Bruce.
- (5) It was suggested that the Chairman of the Committee on Fellowships and Awards, through Mr. Loveland, circularize the Regents and Governors, members of the Association of American Physicians, Professors of Medicine throughout the country for suggestions of names for those who should be considered for the Bruce Award and the Phillips' Award immediately after this Annual Session of the College. This is so that information would be available for the June meeting of the Committee on Fellowships and Awards. It was also recommended that Dr. E. Hugh Luckey, who has charge of the Orientation Course for Latin-American Fellows at Cornell, be invited to attend the meeting of the Committee in June.

"After considerable discussion about the effect of the demands of the Armed Forces on the recipients of Fellowships, the following motion was made by Dr. Maurice C. Pincoffs, seconded and passed:

Funds allocated to Fellowships to men who are later called for active duty in the Armed Forces, and, hence, unexpended, should be held in reserve for these men upon discharge from the Armed Forces."

PRESIDENT MIDDLETON: "The last recommendation requires approval by the Board of Regents."

On motion by Dr. Sturgis, seconded by Dr. George H. Lathrope, and unanimously carried, the recommendation of the Committee was approved.

On motion by Dr. Sturgis, seconded and regularly carried, the recommendation of the Committee with regard to the selection of the Phillips and Bruce Medalists by the Committee on Fellowships at a meeting in June was approved with the stipula-

tion that the Executive Committee of the Board of Regents shall finally approve on behalf of the Board of Regents the candidates selected.

On motion by Dr. Sturgis, seconded and unanimously approved, the recommendation of the Committee that the recipient of the Phillips Award shall have all his travel expenses paid to the Annual Session and additionally shall receive an honorarium of \$250.00, in addition to the medal, was accepted.

On motion by Dr. Sturgis, seconded and unanimously carried, the recommendation of the Committee that the Bruce Award be \$400.00 was approved.

A further resolution was adopted, approving the report as a whole.

PRESIDENT MIDDLETON: "This concludes the portion of the session devoted to affairs of the Board of Regents. I declare a brief intermission, after which the meeting will continue with the Governors' division of proceedings, with Dr. Walter L. Palmer, Chairman, presiding."

INTERMISSION

CHAIRMAN WALTER L. PALMER: "The first item on the Governors' section is the report of the Governors' Survey Committee, of which Dr. Charles A. Doan was Chairman, and Dr. Robert Wilson, Jr., and Dr. Dwight L. Wilbur, members."

Dr. Charles A. Doan read the prepared report of the Governors' Survey Committee.

Report of Governors' Survey Committee

"At the Boston Meeting of the Board of Governors last year, there developed another in a series of recurring discussions regarding the establishment of a minimum age limit of 35 years for Associateship in the College. The steadily increasing size of the total membership, resulting in an ever-enlarging attendance at the Annual Meetings associated with space and scientific sessions' complications, has resulted in a common desire among Governors and Regents for a current resurvey of the fundamental objectives of the College, to determine whether there should be any modification in the rules under which the Committee on Credentials now functions. The Board of Governors, therefore, requested the appointment of an 'interim committee' to study these matters and their implications and to bring in a report with recommendations for consideration at the St. Louis meeting in April, 1951.

"It is understandable that opinions should differ widely as to the best methods for solving the problems arising out of the natural growth of our profession and specialty in an expanding American population and economy. Tradition is characteristically resistant and unresponsive to changing circumstance, though without its balancing perspective, seemingly expedient values frequently are mistaken for the more enduring verities. The main question, therefore, is how the College can maintain its originally high standards and qualifications for Fellowship, and coincidentally give recognition to the rapidly growing number of Internists certified by the American Board of Internal Medicine, and demanded professionally by the American public.

"The American College of Physicians is unquestionably today the organization which most nearly represents the high purposes and basic objectives and ideals of the Internists of North America. A great many of our Fellows have expressed the hope that it may not be necessary to place additional barriers or hurdles to affiliation for those physicians, irrespective of age or number, who reflect the true spirit, and fulfill the established requirements for recognition as certified Internists. At the same time, there should be provision within the College for special recognition and honor for outstanding individual accomplishment. Both Associateship and Fellowship are now granted upon the basis of sound character and proven professional competence, rather than demonstrated leadership or outstanding distinction. Applications are accepted from men of high professional reputation, but with full knowledge that they are not, and never expect to be, clinical investigators; yet the scientific publica-

tion of presumably important medical information is required for advancement to Fellowship. The greatest embarrassment to individuals and to the College is now occasioned through inability of many Associates to meet the Credentials Committee's standards for these required publications during the three- to five-year probation period now prescribed, though they continue to serve their respective communities equally as faithfully and scientifically as before. Last year there were 25 invited resignations, and 35 summary notices of separation from the Associate list. This is not unlike a university disavowing a former A.B. graduate and loyal alumnus, because he has failed to achieve a doctorate from the Graduate School in a prescribed period. Either an Internist is professionally worthy of affiliation with the American College of Physicians when he is originally elected or he isn't. To decide differently later, on other than ethical or moral grounds, is more a reflection on our professional organization itself than upon the individual whom we repudiate, unless we profess to be an association of researchers and investigators only. This situation is a matter of acute embarrassment to every Governor who has the best interests of Internal Medicine for his own state or territory strongly upon his conscience. There is an inconsistency in present practice, which must be faced and corrected in one way or another, if the full influence and prestige of this College is to be maintained among the profession, and public good will is to be fostered.

"We, therefore, propose the following modifications of present practice for consideration:

- (1) Since the College originally sponsored and continues to have major representation on the American Board of Internal Medicine, those physicians who have been certified as Internists by this Board, might be considered eligible ipso facto for Associate Fellowship, provided they meet character, residence, and due requirements of the College. Such election would constitute permanent membership without term limitation, except under special circumstances of grave professional misconduct. Under this plan, those who become certified Internists would have the opportunity of supporting and participating in the affairs of the College during their entire active professional career.
- (2) The College would retain its custom of electing 'honoris causae' to Associate or full Fellowship, those physicians and scientists selected for individual specific accomplishments irrespective of certification by the American Board of Internal Medicine.
- (3) Requirements for full Fellowship could then become more selective, so that eventually election to Fellowship would become a distinguished honor, as it now is in the Royal College. Achievement of this distinction could come early or late in the professional career of the individual physician, depending upon the evaluation of his contributions by his peers. The Credentials Committee would be charged with the responsibility of reviewing each year the Associate Fellowship, to determine those most worthy of full Fellowship. Mastership would continue to constitute a still higher honor to deserving Fellows.
- (4) The Regents and the Board of Governors should be particularly charged with the responsibility of encouraging aspirants for graduate training in Internal Medicine, by making provision for their attendance, and, on occasion, participation in the Graduate Course programs, and in the Regional and State meetings under the auspices of the American College of Physicians. The Annual Sessions could then be limited to the membership, due to space limitations, without too much criticism.

- (5) The College, under these circumstances, might desire to undertake the sponsorship of a survey to investigate from time to time the supply and demand for Internists in this country. The results of such surveys should be the only basis upon which any limitation in total membership is based in the future. Specifically, we do not favor or recommend either elective or compulsory emeritus status for Members of this College, as a means of providing for new Associates, as is the custom in other Societies in their attempt to recognize and absorb an ever-growing group of competent peers, but with a limited membership.

"In making the foregoing recommendations, the Committee obviously has been governed, not so much by fears of the actual or potential 'bigness' of the College, as by the keen desire for 'inclusiveness' within one organization of the great majority of physicians specially qualified in Internal Medicine. Any attempts at 'exclusiveness,' will only result in multiple rival or competing organizations within what should be a 'united fraternity.' If provisions for recognition of different types and degrees of accomplishment are made within the broad field of Internal Medicine, with appropriate means for their acknowledgment, we shall have achieved both the democratic principle and the merit reward within one organization, which principles have effectively stimulated maximum individual effort within the democracy we have known in this country since its beginning.

Respectfully submitted,

ROBERT WILSON, JR., M.D., South Carolina

DWIGHT L. WILBUR, M.D., California

CHARLES A. DOAN, M.D., Ohio, *Chairman*"

CHAIRMAN PALMER: "Thank you very much, Dr. Doan, for your very thoughtful, stimulating and beautifully worded report. I know the Governors particularly will wish to give this careful consideration. It also will be of great interest to the Regents, and particularly to the Credentials Committee. In a sense, the Governors are on one side of the fence and the Credentials Committee on the other, because the Governors are always besieged by candidates seeking election. Candidates and their sponsors naturally think the candidate should be within the College, and the Credentials Committee on the other hand is confronted with the problem of trying to maintain and elevate the standards of the College. We are all interested in the same thing in the end, but we probably look at it from a different point of view. Dr. Doan has asked that I request the other two members of his Committee to discuss the proposal, and I will call first upon Dr. Wilson, who is not only a member of Dr. Doan's Committee, but a representative of the Governors on the Credentials Committee."

DR. ROBERT WILSON, JR.: "Mr. Chairman and Gentlemen: In the Minutes this Committee was actually called a committee on limitation of the College and that was intended to be its main function. In the agenda for today, it appears as a survey committee. In his remarks, Dr. Piersol stated that the members of the Credentials Committee had been asked to communicate directly with our Committee as to the meaning of Fellowship in the College. Therefore, we really have a rather large order; first, in determining just what the work of this committee is. I agree fully with Dr. Doan's report as to the limitation of the College. I do not think that limitation of membership, either by a minimum age or by duration as an Associate in the College, is feasible, because ours is an expanding community. We are going to have more doctors; we are going to have more qualified physicians as our population increases, and we are going to have a much larger group of men over the country who should be members of the American College of Physicians.

"I agree pretty fully with Dr. Doan's preamble. There are one or two points with which I do not agree altogether in his conclusions and in his recommendations, but as to the preamble, I think that I agree completely with the presentation.

"I have here letters from each of the six members of the Credentials Committee on what they have regarded as the meaning of Fellowship. I won't read all the letters, because it would take too long, and the members of the Committee didn't hesitate to write long letters, some of which I received only yesterday and was unable to present them to Dr. Doan until this morning; but our main idea has been to try to differentiate the meaning of certification by the American Board of Internal Medicine from the meaning of Fellowship in the College. I think we all agree that certification by the Board indicates that the professional qualifications of the individual, his proficiency and his theory and practice of Internal Medicine and the adequacy of his work, make him a potential man for the practice of good Internal Medicine. We all think also that Fellowship in the College should not merely mean this potentiality, but its actual fruition; that while certification by the Board might well mean a potential, the Fellowship in the College should mean accomplishment and achievement in the practice of Internal Medicine.

"Now, exactly how those things can be translated into ideas and details which the Credentials Committee can decide on and say, 'Is this man a suitable candidate for elevation to Fellowship, or is he not?'—that is the difficult problem on which we members of the Credentials Committee want help and ideas.

"Now, Dr. Doan has suggested that we have an unlimited period for Associateship in the College. That I think is a good point as an alternative plan, though I might make the following suggestions: first, I think we all agree that we shall have much more exacting requirements for election to Associateship in the College. One of the toughest problems which we have is the case of a candidate who has been elected an Associate, his time is running out, he has not been able to meet the requirements for elevation to Fellowship, either by certification or by production and advancement in professional activities, and he must now be automatically dropped. We have heard a long list of Associates read today of this group which has to be dropped. Some of these men probably should never have been elected Associates. The main problem, I think, is exacting increasingly difficult requirements for election to Associateship, and that might be effected by several methods. One would be the requirement of certification before election to Associateship. That would completely obviate the necessity for dropping any one out for failure to attain certification. At present we require certification before election to Fellowship, but not for election to Associateship.

"One objection to this proposal is that our Postgraduate Courses are supposed to provide help for Associates in reaching certification. Then another requirement, a longer time of establishment in one's community, so that the candidate can become better known to the Fellows in his state and community. We had an instance yesterday of a man who was in a certain community; he had excellent letters, but there was one person, in a position to know intimately this man's standing, who revealed that the candidate was not fit to be an Associate or Fellow of the College. Had it not been that this was a candidate for Fellowship and that specific inquiries had been distributed in the man's community, the Credentials Committee would have known nothing about his disqualifications. It is important to require a longer time of establishment in a certain community where the candidate's fellow colleagues can become well acquainted with him.

"Then, we might consider also an increase in the maximal period a man may be an Associate. Perhaps we should not make the Associate term indefinite, but certainly give him longer than five years to qualify for Fellowship. We might also

consider an increase in the minimal term before an Associate becomes eligible to present his credentials for Fellowship.

"There is a general feeling in the Credentials Committee that we need to have some change, although we are not by any means in agreement just what those changes should be. It is important, if the way we are handling this matter now does not work, to try another way, and to try again and again, until we eventually succeed in the way which will be of the greatest benefit to our own institution and to the men who will later be members of the College."

CHAIRMAN PALMER: "Thank you, Dr. Wilson. We should like to hear from Dr. Dwight L. Wilbur, the third member of the Committee."

DR. DWIGHT L. WILBUR: "I believe the report handles all of the many problems that have been pointed out by Dr. Doan and by Dr. Wilson very well. I do not need to discuss them at length. I shall be glad to take up any point about which there may be a question. I am one hundred per cent for the report."

CHAIRMAN PALMER: "We would like to hear from Dr. Piersol, Chairman of the Credentials Committee."

DR. PIERSOL: "Mr. Chairman, having just heard this report, which deals with matters so fundamental and vital, it is a little dangerous to express opinions without careful study. The thing that interests me the most and gives me great gratification is to find, after having fought a losing fight for many years, holding that before an Associate should be elected, he should be certified, and having created a veritable furor in the Board of Governors when that suggestion was brought up some years ago, to find now that this Committee, after due and careful consideration, has come around to exactly the same opinion that the Credentials Committee held more than five years ago. I am still of the opinion that much trouble would be obviated and the best educational criteria possible would be available if no one were elected to Associateship until he be properly certified by the American Board of Internal Medicine, or, if we continue to have the ancillary groups, by the other appropriate certifying Boards. That brings up again the question that, with the rising and growing group of men in Internal Medicine in this country, whether the old plan of admitting men from other fields allied to Internal Medicine, such as Radiology, Pediatrics, Public Health, Dermatology, and so forth, should be continued, or whether the membership should be restricted to internists, as some members of the Credentials Committee now strongly feel, thus to limit the membership of this organization to internists, and to eliminate the current problems of dealing with industrial physicians, dermatologists, toxicologists, and so on. It is a situation which requires definite and fundamental and radical legislation, and I think the basic principles set forth in this report are excellent—particularly the one requiring certification prior to Associateship."

CHAIRMAN PALMER: "May we hear from Dr. Maurice C. Pincoffs?"

DR. MAURICE C. PINCOFFS: "Dr. Doan was kind enough to let me see this report a few days ago, and I was very much impressed with it. I feel, however, that we can only talk about it today in a very general way, because it is a broad, strategic concept and its operational details have not yet been worked out. Basically, the present method of selecting Fellows may not be satisfactory. I think a tremendous amount of devoted work has been given to it, and that under our present policies it operates to the best advantage that those policies permit. However, we are getting into a status where we have too many Fellows for the good of the prestige of the College. In selecting these Fellows by our present methods, I think we lay too much stress upon one aspect of an internist's work or career. That is, the matter of publications. As a result of that, we are forced to drop out of the College every year a very significant number of young internists, and that, I believe, is a danger to our future."

"Something was said in this report of the disadvantages of exclusiveness.

"As the report pointed out, there can readily be built up among the candidates whom we have cast out a group of malcontents, men who feel that perhaps they have not been fairly dealt with, and we might end up with a split among the internists of the country—not now, perhaps, but in ten years from now. That would be very unfortunate. For those reasons, I think there is something to be said for raising the standards of Associateship, from the present status of a mere probationary junior type of membership to a fixed rank in the College, which in time will become the larger numerical group of the College, and to select by much higher standards than we do now men to be elevated to the rank of Fellow. Insofar, I concur with the strategy of the report, but I would like to point out that I do not think it is ready for any action, because of the operational difficulties that exist in it. One could select Fellows by a much higher standard than we now use, but how? The same difficulty as now exists will arise unless a method is devised. We must work out some practical method of determining what these higher standards shall be and how to operate them. We are not ready to adopt the report. Obviously, there would be an interim period in which we would have a body of Fellows selected by simpler standards and a small minority within them selected by very high standards, and implications of that should be thought out before we take action. Furthermore, as our Secretary will agree, some rather careful thought must be given to what effect this would have in alterations in the Constitution and By-Laws, and what effect it would have on the fiscal affairs of the College. I think the objective is good. As a finished program, I think it requires a great deal of further study. I hope that the Board of Governors may continue this Committee to work out a solution of some of the difficulties that the plan would entail."

CHAIRMAN PALMER: "We shall now throw the report open to general discussion."

DR. ALEX. M. BURGESS: "Mr. Chairman, I should like to speak to this report, with the point of view of the American Board of Internal Medicine. In the first place, I would like to congratulate particularly the Board of Governors on this masterly report and the very wise comments we have heard, particularly those of Dr. Pincoffs. For some time I have personally felt that exactly this sort of thing was very much needed. If we build our requirements entirely on certification by the American Board of Internal Medicine, we are to some extent building our house on a foundation of sand. By that I mean that I think any conscientious member of the Board of Internal Medicine will admit that in our written examination there must be about a ten per cent error, and in our orals, somewhat more than that. I believe that we wrongly decide on about ten per cent of the candidates for the written and somewhat more on the candidates for the oral, but I think that is a very good record. I do not believe any other examination by any of the other boards do as well. Now, if that be the case, there are certain people who don't pass the board examinations who should, and I note particularly in Dr. Doan's report that he has left a loophole. In other words, he has suggested that certain candidates may be accepted as Associates on credentials other than certification. Now, for example, we have been talking about the allied specialists in radiology, pathology, pediatrics, etc. What about the associate professor of medicine, a splendid investigator doing a fine job in teaching internal medicine, but who cannot pass the board examinations, because he is primarily an excellent physiologist, perhaps, an excellent teacher, but not a clinician. Many of these men, I think, would be better Fellows of our College than some who are certified, or who are in other specialties. In other words, I think we ought to have the possibility of selecting certain people who come up to our Fellowship standard, or our Associate requirements, who are not necessarily clinicians, as is required by the Board of Internal Medicine. We shall have to give this a great

deal of consideration from that point of view. Our ideals, just as Dr. Doan has described them, should be, first that a man who is certified by the Board of Internal Medicine is certified to be a competent internist and may be entitled to Associateship, but that a Fellow should be a distinguished and experienced internist."

DR. PAUL F. WHITAKER: "I think this problem is so fundamental and so important, as Dr. Pincoffs has so well pointed out, that it is a matter that should not be acted upon hastily. I certainly commend the language of the report, and I would like to make the suggestion that this report be sent to every member of the Board of Governors as a basis for their own thinking, perhaps, with a request that each member of the Board of Governors give it their individual thought and write Dr. Doan's committee the benefit of their opinion and thinking."

CHAIRMAN PALMER: "Dr. Doan points out that copies have been given to each Governor at this meeting. The report may be discussed further by the Governors at their next meeting on Wednesday, or action can be taken now, whatever is desired."

DR. DOAN: "Mr. Chairman, I would like to add that it was not our thought that this is ready for immediate action. As I understood the appointment of this Committee, we were to solicit the thoughts and suggestions of the members of the Board of Governors and of the Board of Regents; we were to bring in a target at which to shoot. We received a great deal of comment and much correspondence has passed between my office and different members of the College. This report is presented for consideration as a background and basis for discussion. There are many details that would need to be considered, most of which I think our Committee has thought about, but which we did not feel pertinent to this initial presentation. If this report is acceptable in general as a matter of principle, then, of course, the details would necessarily need to be worked out."

CHAIRMAN PALMER: "Dr. Doan, if the principles propounded in your report were adopted, what in your judgment would be the effect on the size of the College?"

DR. DOAN: "That would need to be discussed in terms of the policy of the American Board of Internal Medicine to some extent. The American Board requires a certain period of time before examinations can be taken. There are lapsed periods of that time that are required, and we should have the benefit not only of the careful screening of the American Board of Internal Medicine, but such additional screening as our Credentials Committee might follow. The Committee has not attempted to direct the Committee on Credentials as to minimal requirements."

DR. LEMUEL C. MCGEE: "I should like the Governors to keep in mind these suggestions in their reflections on this proposal, because I did not understand myself until I served three sessions on the Credentials Committee. I had heard that there had been great emphasis on the character and number of publications required. I have discovered from experience that actually there is no great emphasis placed on the number and character of publications. This requirement actually has been de-emphasized to the point that it is surprising what a minimal number of papers, sometimes low in importance, may be accepted and not held against the candidate, if his other credentials are good and he has the right type of recommendations and backing of his Governor and local Fellows. In a number of instances, publications were entirely lacking, but the Credentials Committee accepted gladly the man's effort in the form of a thesis, provided he had shown signs of growth and improvement during his Associate term."

DR. WILBUR: "If the Board of Governors does not wish to take any action on this proposal today, I suggest the Committee be asked to meet again in the interval between now and the next meeting of the Board of Governors on Wednesday, and that at that meeting the Governors consider this more fully. Members of the Board have this proposal now in writing and will have a chance to review it. A number of problems may arise that have not been considered."

CHAIRMAN PALMER: "If no one objects, this Committee is requested to meet again between now and the next meeting, and to present at that time a further report to the Board of Governors."

DR. HUGH J. MORGAN: "Mr. Chairman, I get the distinct impression that it has been suggested that maybe this College would automatically elect a candidate to Associateship who has passed the American Board of Internal Medicine examinations. I think it would be very serious if any one left this room with any such idea, and I would decry that notion, if any one has it."

DR. DOAN: "There is no thought of that."

CHAIRMAN PALMER: "The next item on our agenda refers to our Regional Meetings. The Secretary has distributed a report on all the Regional Meetings for the past year. Is there any question or problem with regard to them, which should come up for discussion?"

PRESIDENT MIDDLETON: "Mr. Chairman, I rise simply to comment upon the experience of one Regional Governor in Kansas. There is a very active regional group and without casting aspirations or making comparisons, a lot of the activity is dependent upon the contributions of the Governor, who has made it his purpose and design not only to keep in constant contact with the members, but also to afford them and particularly those who have not attended Regional Meetings, a news letter, an abstract of the papers that have been given at such meetings. I leave this with the other Governors as a source of stimulation."

CHAIRMAN PALMER: "Mr. Loveland, would you like to speak on the subject of the Regional Meetings?"

SECRETARY LOVELAND: "There is one matter in particular that I would like to emphasize. With the growing number of these Regional Meetings, it is highly desirable that Governors schedule their meetings longer in advance. There is the problem of obtaining the speaker, an Officer or Regent of the College. Conflicting meetings, or meetings scheduled too close together, oftentimes put undue hardships on those who are asked to attend as representatives of the Board of Regents. During the past year some of our Officers, particularly President Middleton and President-Elect Pincoffs, have traveled to far distant points, across the country, and in one instance to Puerto Rico. Dr. Middleton particularly has given most generously of his time and thought to these Regional Meetings and has attended a large proportion of them. Many of the Governors have already scheduled their autumn, 1951, meetings, and others who are planning such meetings are urged to register dates and plans promptly with the Executive Office."

DR. JOHN MINOR: "Mention has been made of the stimulation and participation in these Regional Meetings of the younger men, men who are not necessarily already Associates, but who are obviously potential candidates. I think we should all in our regional meetings make every effort to have the program a 'young program,' not just an effort of selecting visiting firemen and prominent persons, but to give every opportunity to developing younger men to present their work."

DR. MIDDLETON: "My comments are merely a testimonial that for one who has had the opportunity of the last two years to observe the enthusiasm and efficiency of the Regional Meeting, I believe this program is second only to the Postgraduate Courses in the total educational program of the College. The opportunity to go among the different groups from every section of the country, to partake of the clinical, experimental and other phases of the programs and to observe at first-hand just what a group is doing locally, to see a young man in a small community practicing internal medicine on a plane that would give pride to any teacher, and working out the intimate details of what he termed periarteritis nodosa and such, to see other men in rather removed areas doing clean-cut clinical research on ordinary medical problems, comparing very well with the work that appeared in other quarters and medical

school centers, is to give you the type of uplift that you need if you are going to do this job. It is my firm conviction that this particular effort of the College in helping men get ahead is to the complete credit of this organization."

DR. PINCOFFS: "I have found it very stimulating to attend the Regional Meetings, and I feel they are a very important part of the College work, a testimonial to our Governors, as well as to our members. If I were to make any comment on the programs, interesting as I have found them, it would be that for men in practice a little more stress in some meetings on the purely clinical as opposed to the investigative side would make them even more valuable."

DR. MIDDLETON: "I think when you go into more of the grassroot areas, North Dakota, or down to Mississippi, you will find that they are speaking purely of clinical subjects, and the young men are putting it on the line."

DR. EDWARD C. KLEIN: "In regard to the problems of scheduling Regional Meetings, I would like to recommend that other Governors consider what we are doing in New Jersey, namely establishing a fixed date for our Regional Meetings every year. This will allow not only the incumbent, but future Governors plenty of time to know how to arrange for his program."

Following various announcements, read by the Secretary, Chairman Palmer declared the meeting adjourned.

Adjournment,

Attest: E. R. LOVELAND,
Secretary

ABSTRACTED MINUTES ANNUAL BUSINESS MEETING

ST. LOUIS, Mo.

APRIL 12, 1951

The 1951 Annual Business Meeting of the American College of Physicians was held in the Opera House of the Kiel Auditorium, St. Louis, Mo., at 2:00 p.m., Thursday, April 12, President William S. Middleton presiding.

PRESIDENT MIDDLETON: "The Annual Business Meeting will be in session, a quorum is declared. The Secretary will read abstracted Minutes of the last Annual Business Meeting in Boston."

Mr. E. R. Loveland read abstracted Minutes of the preceding Annual Business Meeting, which were approved as read.

PRESIDENT MIDDLETON: "The Treasurer, Dr. William D. Stroud, will present the annual report of the Treasurer."

DR. WILLIAM D. STROUD: "Mr. President, Masters and Fellows of the College: the detailed statements of operation of the College for 1950, along with the certified public accountant's report, will be published in an early issue of the *ANNALS OF INTERNAL MEDICINE*.

"During the year 1950 the College added to its General Fund \$72,609.57; to its Endowment Funds, \$26,633.78; total, \$99,243.35.

"The gross assets of the College, as of December 31, 1950, amounted to \$766,902.50, divided as follows:

General Fund	\$412,298.25
Endowment Fund	333,833.42
James D. Bruce Fund	10,395.83
A. Blaine Brower Fund	10,375.00
	<u>\$766,902.50</u>

"The College operated wholly within its budget. In fact, the income exceeded budgetary expectations, whereas expenditures did not exceed appropriations of a year earlier. The investments of the College are supervised by an investment counselor and by the Committee on Finance and are carefully reviewed periodically. As of December 31, 1950, the College held Investments at Book Value totalling:

Endowment and Restricted Funds	\$349,259.87
General Fund	266,485.35
	<u>\$615,745.22</u>

and as of last November showed an appreciation of \$48,887.00, and the average yield at that time was 4.58%.

"The Board of Regents has approved a budget for 1951 calling for an estimated income of \$286,600.00 and an estimated expenditure of approximately \$256,670.00, leaving an estimated balance of approximately \$29,900.00.

"The financial policies of the College continue to be conservative at all times.

Respectfully submitted,

WILLIAM D. STROUD, *Treasurer.*"

By motion regularly seconded and carried, the report of the Treasurer was accepted.

PRESIDENT MIDDLETON: "We will now have the annual report of the Executive Secretary, Mr. Edward R. Loveland."

MR. EDWARD R. LOVELAND: "Mr. President, Fellows and Masters of the College: The report of the Executive Secretary is supplementary to those of the President, the Treasurer and the Secretary-General."

"If I may, I should like this year to make a comparative report and summary, covering not only the year 1950, but comparing it with 1926, twenty-five years ago, when I first became affiliated with the College. We cannot say 1950 was more significant in the College than 1926 just because the activities were so much more numerous and diversified. In reviewing 1926, we have noted that while the activities of the College essentially were restricted to the passing on candidates for Fellowship, on publishing a journal, then known as the *ANNALS OF CLINICAL MEDICINE*, with a circulation of about 1,200 copies monthly, and the conduct of the Tenth Annual Clinical Session, the internal changes then contemplated were very significant. Dr. Alfred Stengel and his associates were at that time completely reorganizing the College. Plans had been consummated for the merging of the American Congress on Internal Medicine with the College, the members of the Congress to become the original nucleus of Associates in the College. Far-reaching changes were made in the Constitution and By-Laws; more definite entrance requirements were specified; definite terms of office were indicated for Governors, Officers and Regents; the Credentials Committee was formally organized and the standards of membership more clearly stated; Life Membership was instituted and the first two Life Members were enrolled during the Annual Session that year in Detroit; the College Headquarters was moved from Chicago to Philadelphia; it was a year of enthusiastic planning. To that time the total funds of the College amounted to some \$18,000.00 and the membership was approximately 1,000 Fellows.

"All through the succeeding years a constructive and yet conservative program has gradually expanded the activities of the College many fold. In spite of ever increasing standards for membership in the College, the Fellowship Roster has increased to 5,212, the Mastership Roster to 14, and the Associateship Roster to 1,856, or a total of 7,082. It may be observed that there is comparatively a small number of those original one thousand Fellows now living. The journal, since 1927 known as the *ANNALS OF INTERNAL MEDICINE*, has increased in its stature and in its circulation, the latter from the original 1,200 in 1926 to some 14,750. The Annual Session attendance has grown from less than 1,000 in 1926 to over 5,000. The finances of the College have increased from the \$18,000.00 in 1926 to \$766,900.00 at the end of 1950. Incidentally, dues and fees in the College are the same today as they were in 1926.

"We have added a national program of Regional Meetings; we have instituted Postgraduate Courses, with a registration of more than a thousand physicians every year; we have established Research Fellowships, Latin-American Fellowships, Traveling Fellowships, and other far-reaching programs, such as those associated with the Council on Medical Education and Hospitals of the American Medical Association, in regard to residencies and hospital certification. Even in the last decade our gross membership has increased 60%, our Life Membership, 553%; our Endowment Fund, 203%; the circulation of our journal, 159%; the attendance at our Annual Sessions, 87%; the growth in our Regional Meetings, 900%; the registration in our Postgraduate Courses, 630%; our annual appropriation for Fellowships, 300%.

"A very important comparison, between 1926 and 1951, should be made with respect to our College Headquarters. In 1926 we first occupied in Philadelphia a two-room suite and had a total of three employees. Today we own and occupy a beautiful and adequate Headquarters Building, with a staff of fourteen employees there, exclusive of those in our Editorial Office in Baltimore.

"In late 1949, the College published the first post-war Directory and during 1950 a Supplement thereto. The Directory will be completely revised and republished during the current year, this being authorized by the Board of Regents at a meeting in November, on condition that members may subscribe at the lower than cost rate of \$4.00, with the exception of Life Members, who shall receive it without charge.

"All through the years and certainly during this past year, we have appreciated deeply the sympathetic and ready coöperation and advice not only of the Officers, Regents and Governors of the College, but of the members-at-large. We have never known any organization of any character in which its directing bodies, serving totally without recompense, have so unselfishly given their time, service and thought, and I want especially in this report to express my appreciation to President Middleton, Secretary-General Piersol, General Chairman Kinsella, and others, who have assisted me so much during this past year.

"We have just received from the Registration Desk a report that the total registration to this time at this meeting is 3,259, of which 475 are ladies.*

Respectfully submitted,

EDWARD R. LOVELAND, *Executive Secretary.*"

On motion made, seconded and regularly carried, the report of the Executive Secretary was accepted.

PRESIDENT MIDDLETON: "I ask that on the twenty-fifth anniversary of the services of our Executive Secretary that we stand in respect to him. (Applause) We shall now have the report of the Secretary-General, Dr. George Morris Piersol."

DR. GEORGE MORRIS PIERSOL: "Mr. President, Regents and Governors, Masters and Fellows of the College: This report will be limited to certain important matters of especial interest to you.

"*Membership*—Since the last Annual Session of this College, there have been elected 1 Master; 326 Fellows; 400 Associates, which brings the total membership to the following:

Masters	14
Fellows	5,212
Associates	1,856
Total	<u>7,082</u>

"*Life Members*—During the past year 64 Fellows have become Life Members of the College, bringing the total to 927, of whom 90 are deceased, leaving a balance of 837.

"*Deaths*—During the past year we have lost by death 85 Fellows and 14 Associates. Their names and records are recorded in the Archives of the College, and in almost every instance, the obituaries have been published in the ANNALS OF INTERNAL MEDICINE.

"*Postgraduate Courses*—The Advisory Committee on Postgraduate Courses of the Board of Governors and the Committee on Educational Policy of the Board of Regents organized and conducted during 1950 a total of sixteen (16) courses, with a registration of 1,071 physicians. The Committee is attempting to improve the

* Final Analysis of Registration:

Members	1,564
Guest Physicians	720
Guest Non-Physicians	23
Students	13
Exhibitors	464
Ladies	475
	<u>3,259</u>

quality of instruction, to expand the field of study and to increase and diversify the institutions and geographical locations where the courses are given. This program is one of the most popular and valued activities of the College.

"Fellowships"—The College is maintaining at the present time six (6) Research Fellowships, and has voted six (6) new Research Fellowships to start July 1, 1951. The annual budget of this particular program is now \$20,500.00. The work of the fellows and the end results are carefully observed, with a view to evaluating the program and to act as a guide in the future.

"The College also has sixteen (16) Latin-American Fellows presently working in this country, this program being carried on in co-operation with the W. K. Kellogg Foundation, who furnish the funds. This program affords an unique opportunity for the training of Latin-American young men for careers of teaching and research in their homelands.

"Regional Meetings"—Considerable impetus has been given to State and multi-State Regional Meetings. In 1950, most of the United States and parts of Canada were covered by these interim gatherings. Twenty-three (23) such meetings were held during the calendar year 1950 and sixteen (16) have either already been held, or are definitely scheduled during the current year. It is anticipated many more will be added. The attendance at these meetings during 1950 was:

Members	1,811
Non-Members	1,236
Total	<u>3,047</u>

"Of greatest significance to the membership-at-large is the Annual Session of the College. This Session in St. Louis is a further outstanding example of the accomplishments of a year's coördinated effort. We are mindful and appreciative of the great efforts of those who have made this, the 32nd Annual Session of the College, possible.

Respectfully submitted,

GEORGE MORRIS PIERSOL, *Secretary-General.*"

On motion seconded and regularly carried, the report of the Secretary-General was approved.

DR. PIERSOL: "Now, President Middleton, you have guided the destiny of this organization for the past year and have carried out its purposes with good judgment and exceptional ability. We, who have had the privilege of being closely associated with you in the conduct of the College, are keenly aware of the never failing courtesy, coöperation and forbearance that have marked your every act. It is, therefore, our desire to express to you in some enduring manner our appreciation and affection on behalf of the Fellows of the College, the Officers, the Regents and the Governors of the American College of Physicians, and it is our pleasure at this time to present to you this Gavel." (Applause.)

PRESIDENT MIDDLETON: "Dr. Piersol, I wish to thank every one very kindly. Mine has been an unusual opportunity in the past year. You may recall that on assuming office in Boston last year, I spoke of the coöperation and the increased support of the Fellows of the College. I have had it to the fullest measure during my Presidency. I wish on this occasion to express my appreciation to the Secretary, to the Officers who have abundantly supported my hand, to the entire Fellowship throughout the country. I took your mandate that it was my responsibility to get about, and as a result I think there are very few members among you who will have quite the grasp of the national picture that I have. I can assure you that the American College of Physicians is a going and a growing concern, of which you can be very proud.

"My successor, Dr. Maurice C. Pincoffs, has been a doer of good, and a doer of good in this College for many years. His association with the College dates from 1923; he has held many offices, the Governorship, Regency, Vice Presidency. Dr. Pincoffs has had a distinguished academic career at the University of Maryland, where he is Professor of Medicine and Head of that Department. He has been very active in the affairs of the state, having served on several occasions in relation to public health matters in Maryland. Furthermore, he has a very distinguished military career. He has served in both World Wars, and has distinguished himself in these vocations. In the post-war period he has found activity beyond his ordinary academic circles in the area of the Armed Forces Medical Advisory Committee, a most important Committee known to most of us as the Cooper Committee, where his talents have been particularly effective.

"However, Dr. Pincoffs' particular outlet in the affairs of the College has been in the Editorship of the *ANNALS OF INTERNAL MEDICINE*. Since January, 1933, Dr. Pincoffs has been Editor of our journal. Under his guidance, this periodical has come to international position and leadership among journals of like objectives. I believe that the unearned dividends that have come in increased prestige in the area of medical periodicals and medical education through the *ANNALS* will go down to the credit of the College itself. In turning then to Dr. Pincoffs, I am in no sense feeling a pressure of a succeeding order. You are passing the Presidency into the hands of a true medical statesman. Dr. Pincoffs."

DR. MAURICE C. PINCOFFS: "Officers, Regents, Fellows and Masters of the College: The Presidency of the American College of Physicians carries serious responsibilities of the President to the members. One of those responsibilities, which I place high in order, is that which relates to General Sessions. The President, as you know, is responsible for the program of the General Sessions and of the Morning Lectures, and he customarily nominates the General Chairman to the Board of Regents, who in turn carries a heavy load for organizing the Clinics and Panels and in providing for those numerous adjunct activities, transportation, entertainment, publicity and so on, which are so essential to the success of the meeting.

"The excellent attendance through the years at your Annual Sessions is a test that the previous President and General Chairman have fulfilled superbly these responsibilities. My efforts in these directions will be to make the next meeting in Cleveland at least worthy of my predecessor. My ambition, of course, is to screen the most significant new scientific developments, with the help of many, thus to select a program which will make every member desire to leave home. I ask you members of the College, to aid me in this undertaking. I ask you to write to me what you want to hear at the General Sessions and I shall want to consult often with many of you.

"The growth of our specialty, Internal Medicine, has presented the College with many serious problems relating to residency and postgraduate training in Internal Medicine, to the standards and technics of the examinations of the certifying boards, to the qualifications for Associateship, to the duration of the Associate term and to the requirements for advancement to Fellowship. The College, as an important educational body in this country, must make its voice heard and its influences felt in decisions affecting professional training of internes and residents who will one day become our future members. It must continue in each of its meetings and in its Postgraduate Courses to offer tangible opportunities to this group. As to the number of aspirants for membership in the College, as membership increases, the College must adapt itself, its policies on admission, so as to avoid on one hand the fault of too great exclusiveness, and on the other, the loss of an incentive to join which would follow a low rate of standards.

"Your governing bodies, the Board of Regents and the Board of Governors, are actively engaged in the study of these responsibilities and problems of the College. What is to be sought is not a radical change in the character or in the functions of the College, this great medical organization which we have inherited, but such evolutionary adaptations as will strengthen the College for its great task of constantly elevating and bettering the quality of medical service." (Applause.)

(Dr. Pincoffs now assumes the Chair.)

PRESIDENT PINCOFFS: "We shall now proceed with the order of business for this meeting. First is the report of the Committee on Nominations by Dr. Alex. M. Burgess, Chairman."

DR. ALEX. M. BURGESS: "Mr. President, the Committee on Nominations, appointed in accordance with the Constitution of the College, places in nomination the following names for the Elective Officers of the College:

President-ElectDr. T. Grier Miller, Philadelphia, Pa.
First Vice PresidentDr. LeRoy H. Sloan, Chicago, Ill.
Second Vice PresidentDr. Walter B. Martin, Norfolk, Va.
Third Vice PresidentDr. Howard P. Lewis, Portland, Ore."

PRESIDENT PINCOFFS: "You have heard the nominations from the Nominating Committee for the Elective Officers. Are there any nominations to any of these offices from the floor? (Pause.) If not, the Chair will entertain a motion for the election of the nominees as read."

On motion made and seconded by several and carried, the nominations were closed and the Secretary instructed to cast a unanimous ballot for the nominees.

PRESIDENT PINCOFFS: "I declare Dr. T. Grier Miller, President-Elect; Dr. LeRoy H. Sloan, First Vice President; Dr. Walter B. Martin, Second Vice President; and Dr. Howard P. Lewis, Third Vice President."

DR. BURGESS (continuing): "The Committee places in nomination the following five names for election as Regents of the American College of Physicians, for a term expiring in 1954. The Committee received a letter from Dr. Middleton, expressing the desire not to be nominated to the Board of Regents, placing this desire on his conviction that the succession of the retiring President to the Board of Regents is not in the best interest of the College.

Dr. Marion A. Blankenhorn, Cincinnati, Ohio
Dr. Asa L. Lincoln, New York, N. Y.
Dr. J. Owsley Manier, Nashville, Tenn.
Dr. Walter L. Palmer, Chicago, Ill.
Dr. Wallace M. Yater, Washington, D. C."

PRESIDENT PINCOFFS: "You have heard the nominations for Regents, for terms expiring in 1954. Are there any nominations from the floor? (Pause.) If not, the Chair will entertain a motion for the election of these Regents."

On motion seconded by many and carried, the nominations were closed, and the Secretary instructed to cast the ballot for the unanimous election of the above candidates, and President Pincoffs declared them duly elected.

DR. BURGESS (continuing): "The Committee places in nomination the following name for election as a Regent of the American College of Physicians, for term expiring in 1952, to conclude the unexpired term of Dr. T. Grier Miller:

Dr. Dwight L. Wilbur, San Francisco, Calif."

PRESIDENT PINCOFFS: "Are there any nominations from the floor? (Pause.) If not, may we have a motion for the election of the nominee?"

On motion seconded and regularly carried, the Secretary was instructed to cast a unanimous ballot for the election of Dr. Dwight L. Wilbur as a Regent, for term expiring in 1952, and President Pincoffs declared him so elected.

DR. BURGESS (continuing): "The Committee places in nomination as Governor for Mexico, for term expiring in 1952, to conclude the unexpired term of Dr. Francisco de P. Miranda, deceased, the name of:

Dr. Ignacio Chavez, Mexico City, D. F."

On motion seconded and unanimously carried, the Secretary was instructed to cast a unanimous ballot for the election of Dr. Ignacio Chavez, and President Pincoffs declared him elected.

DR. BURGESS (continuing): "The Committee places in nomination the names of the following men as Governors of the American College of Physicians, for term expiring in 1954:

Dr. E. Dice Lineberry, Birmingham ... ALABAMA
 Dr. Leslie R. Kober, Phoenix ARIZONA
 Dr. Lemuel C. McGee, Wilmington DELAWARE
 Dr. William C. Blake, Tampa FLORIDA
 Dr. Carter Smith, Atlanta GEORGIA
 Dr. Richard P. Howard, Pocatello IDAHO
 Dr. Howard Wakefield, Chicago ILLINOIS (Northern)
 Dr. J. Murray Kinsman, Louisville KENTUCKY
 Dr. Richard S. Hawkes, Portland MAINE
 Dr. R. Carmichael Tilghman, Baltimore . MARYLAND
 Dr. Laurance J. Clark, Sr., Vicksburg .. MISSISSIPPI
 Dr. Harold W. Gregg, Butte MONTANA and WYOMING
 Dr. Walter I. Werner, Albuquerque NEW MEXICO
 Dr. Irving S. Wright, New York NEW YORK (Eastern)
 Dr. Charles A. Doan, Columbus OHIO
 Dr. Merl L. Margason, Portland OREGON
 Dr. David W. Carter, Jr., Dallas TEXAS
 Dr. Karver L. Puestow, Madison WISCONSIN
 Dr. Rafael Rodriguez-Molina, San Juan . PUERTO RICO
 Dr. John W. Scott, Edmonton ALBERTA and BRITISH COLUMBIA
 Dr. Charles H. A. Walton, Winnipeg .. MANITOBA and SASKATCHEWAN."

PRESIDENT PINCOFFS: "You have heard the names of candidates nominated to the Board of Governors, for term expiring in 1954. Are there nominations from the floor? (Pause.) If not, I will entertain a motion."

On motion seconded by several and unanimously carried, the Secretary was instructed to cast a ballot for the election of all nominees as Governors, and President Pincoffs declared them duly elected.

DR. BURGESS (continuing): "The Committee places in nomination as Governor for Northern California, for term expiring 1953, to conclude the unexpired term of Dr. Dwight L. Wilbur:

Dr. Stacy R. Mettier, San Francisco, Calif."

PRESIDENT PINCOFFS: "Are there any nominations from the floor? (Pause.) If not, may I have a motion to elect Dr. Mettier?"

On motion seconded and regularly carried, the Secretary was instructed to cast a ballot for the election of Dr. Stacy R. Mettier as Governor, for term expiring 1953, and President Pincoffs declared him duly elected.

DR. BURGESS (continuing): "The Committee on Nominations wishes to announce that under provisions of the By-Laws, providing that the Surgeon General of the United States Navy and the Medical Director of the United States Veterans Administration shall be members of the Board of Governors, representing those Services, that

Admiral Herbert Lamont Pugh, (MC), USN,

will at this time become the official Governor of the United States Navy, and that

Admiral Joel Thompson Boone, (MC), USN, Ret'd,

will at this time become the official Governor of the United States Veterans Administration.

Respectfully submitted,

Alex. M. Burgess, *Chairman*

Walter B. Martin

Charles A. Doan

Edward C. Reifenstein, Sr.

Charles E. Watts."

PRESIDENT PINCOFFS: "I shall now appoint Dr. Ernest H. Falconer and Dr. A. B. Brower to escort the President-Elect to the platform."

DR. T. GRIER MILLER: "Mr. President, Masters and Fellows of the College: At this time I can only thank you for the honor you have conferred upon me. I wish to assure you that as President-Elect I shall do my utmost to maintain the high standards set by my predecessors in this office." (Applause.)

PRESIDENT PINCOFFS: "Newly-elected Governors who have not served previously, or other Governors who may be interested, are invited to meet immediately after this afternoon's General Session in Room B of the Kiel Auditorium with the Chairman of the Committee on Credentials, the Chairman of the Board of Governors, the President of the College and the Executive Secretary.

"I am also instructed to announce that the 1952 Annual Session will be held in Cleveland, Ohio, April 21-25, inclusive.

"I will now entertain resolutions."

DR. CYRUS C. STURGIS: "Mr. President, I move the adoption of the following Resolution of Thanks to our retiring President and to our Hosts in St. Louis:

"To our distinguished leader and President, Dr. William S. Middleton, for the inspiration of his guidance during the past year, as well as during this Annual Session;

"To his Chief of Staff, General Chairman Ralph A. Kinsella, for a magnificent program;

"To the Chairmen of their local Committees:

Dr. Daniel L. Sexton, Chairman of the Committee on Auditorium

Dr. W. Barry Wood, Jr., Chairman, and

Dr. Carl V. Moore, Co-Chairman, Committee on Hospital Clinics

Dr. Paul O. Hagemann, Chairman, Committee on Televised Clinics

Dr. Alphonse McMahon, Chairman, Committee on Entertainment

Dr. Alfred Goldman, Chairman, Committee on Transportation and Hotels

Dr. Goronwy O. Broun, Co-Chairman, and

Dr. Harry L. Alexander, Co-Chairman, Committee on Panel Discussions

Dr. Raymond O. Muether, Chairman, Committee on Publicity,

and to the individual members of each of those Committees;

"To Mrs. Anthony B. Day, Chairman of the Committee on Ladies' Entertainment, and all of her worthy and capable colleagues;

"To Mr. Frederick H. Rein, Secretary and General Manager of the St. Louis Convention and Publicity Bureau;

"To all of these and many others, individually and collectively, our heartfelt thanks again for their manifold contributions to the success of this memorable meeting and for their most generous hospitality."

The motion was seconded by many.

PRESIDENT PINCOFFS: "We shall indicate our approval by standing and applauding those people." (Applause.)

"There appears no new business, and I declare this Annual Business Meeting adjourned."

Adjournment.

Attest: E. R. LOVELAND,
Secretary

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